Clinical Study Protocol

NCT Number: NCT03196427

Title: A Phase 2b, Extension Study to Determine the Long-term Safety of Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn's Disease

Study Number: Vedolizumab-2005

Document Version and Date: Amendment 8, 27 Sep 2024

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL

A Phase 2b, Extension Study to Determine the Long-term Safety of Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn's Disease

Long-term Safety With Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn's Disease

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue, Lexington, MA 02421		
Study Number:	Vedolizumab-2005		
IND Number:	009125	**EU CT Number:**	2023-507766-35
Compound:	Vedolizumab IV		
Date:	27 September 2024	**Amendment Number:**	8

Amendment History:

Date	Amendment Number	Region
27 September 2024	8	Global
08 March 2023	7	Global
01 December 2021	6	Global
24 August 2018	05	Global
13 February 2018	04	Global
13 October 2017	03	Local/United Kingdom
25 May 2017	02	Global
07 April 2017	01	Global
17 October 2016	Initial version	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

Takeda Development Center Americas, Inc. (TDC Americas)-sponsored investigators per individual country requirements will be provided with an emergency medical contact information card 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/Rest of World TDC Contact**
Serious adverse event and pregnancy reporting	*Americas:* Fax: +1-224-554-1052 Email: PVSafetyAmericas@takeda.com *Europe/Rest of World:* PharmacovigilanceMailbox@takeda.com
Medical Monitor (medical advice on protocol and compound)	PPD , MD PPD – GI Global Clinical Science Telephone: PPD
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD , MD PPD , Clinical Science Telephone: PPD

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- Regulation (European Union [EU]) No. 536/2014 of the European Parliament and of the Council.
- Ethical considerations for clinical trials on medicinal products conducted with minors.
- Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No. 536/2014 on clinical trials on medicinal products for human use. 2017.
- 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 , MD PPD , Clinical Science	Date	PPD PPD , GI2 Statistics Statistical and Quantitative Sciences, Data Sciences Institute	Date
PPD PPD , Quantitative Clinical Pharmacology	Date	PPD PPD , Pharmacovigilance	Date

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.
- ICH, E6 GCP: 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.
- Responsibilities of the Investigator (Appendix B).

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 8 Summary of Changes

Protocol Amendment 8 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 8. The primary reasons for this amendment are to:

- Comply with European Union (EU) Clinical Trial Regulation (CTR) protocol requirements.
- Update treatment-emergent adverse events (TEAEs) definition.
- Harmonize serious infections adverse event of special interest (AESI) definition across the vedolizumab program.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 1.1 Contacts	Contact information was updated and consolidated for ease of use.	
2.	Section 1.2 Approval	• A statement that the clinical trial will be conducted in compliance with Regulation [EU] No. 536/2014 was added. • A statement that the clinical trial will be conducted in compliance with "Ethical considerations for clinical trials on medicinal products conducted with minors", and "Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No. 536/2014 on clinical trials on medicinal products for human use. 2017." was added.	To comply with EU CTR protocol requirements.
3.	Signatories	The name of the responsible Takeda medical officer and other signatories were updated.	
4.	Title Page Section 2.0 Study Summary	Replaced EudraCT number with EU CT number to comply with EU CTR protocol requirements.	To comply with EU CTR protocol requirements.
5.	Section 3.1 Study-Related Responsibilities	Revised study related responsibilities.	Revised for clarity.

Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
6.	Section 3.5 Study Definitions	Definitions of 'Study start', 'End of study', and 'Enrollment' were added.	To comply with EU CTR protocol requirements.
7.	Section 4.1.3 Vedolizumab IV • Subsection 4.1.3.2 Clinical	Revised 'over 70 countries' to 'more than 70 countries'.	Revised for clarity.
8.	Section 2.0 Study Summary Section 4.4 Risks Associated With Study Procedures	The potential benefit/risk in the boxed protocol summary and benefit/risk section of the protocol with the potential risks for subjects exposed to the investigational medicinal product in the current trial were added.	To comply with EU CTR protocol requirements.
9.	Section 7.3 Excluded Medications, Vaccinations, Procedures, and Treatments	The following statement was added: "Subjects who do not respond to treatment or show worsening of their disease after entering the safety follow-up period will no longer need to abstain from the medications that were prohibited during the screening and treatment periods. High dose glucocorticoids and other treatments will be allowed. Biologics or nonbiologic immunosuppressants should not be initiated during the safety follow-up period without prior discussion with the sponsor study physician or designee due to the long half-life of vedolizumab."	For clarity on whether starting other therapies during the safety follow-up period would be permitted or not.
10.	Section 8.1.2 Storage	Instruction was added to protect the study drug from light.	Clarification regarding study drug storage.
11.	Section 9.1 Study Procedures • Subsection 9.1.2 Demographics, Medical History, and Medication History Procedure	Revised the demographic information that will be collected at screening.	Revised for clarity and to comply with EU CTR protocol requirements.
12.	Section 9.1.6 Efficacy Measurements • Subsection 9.1.6.1.2 CD Activity	Removed the specific visit window and referred to the Schedule of Study Procedures table to align with the changes made in the table.	Revised for consistency between sections.

Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
13.	Section 9.1 Study Procedures • Subsection 9.1.8 Tanner Stage Evaluation	Added visit window.	Added for consistency between sections.
14.	Section 9.1.16 Pregnancy	Incorporated follow-up of all pregnancies and pregnancy outcomes for 1 year after birth.	Incorporated postpartum safety evaluation period to provide additional information on pregnancy outcomes.
15.	Section 9.1.17 CCI [redacted] Appendix A Schedule of Study Procedures	• CCI [redacted]	Added for clarity.
16.	Section 9.3.2 Final Visit or ET Section 9.3.3 Final Safety Follow-up Visit	• Clarified that the final visit is to be completed within 8 weeks following a pre-agreed-upon subject's last dose (determined by the investigator) and prior to any planned dose if the subject is to transition to commercial drug or other drug access program. Subjects are still expected to complete both the final safety follow-up visit (Section 9.3.3), which is performed at 18 weeks post-last dose, and the long-term follow-up safety survey (phone call), which is completed 6 months after the last dose of study drug (Section 9.3.4). • A statement "Subjects are expected to complete the final safety follow-up visit." was added.	Revised for clarity.
17.	Section 9.3.5 Poststudy Care	Revised the statement from, 'Posttrial access to vedolizumab IV may be provided by the sponsor' to 'Posttrial access to commercially available vedolizumab IV may be provided by the sponsor'.	Revised for clarity.

Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
18.	Section 9.3.8 Alternative Approaches to Study Procedures and Data Collection Due to a Pandemic	The following statement has been removed: "AEs of COVID-19–related disease and COVID-19 pneumonia are now included as medically significant AEs (see Table 10.b)". These will continue to be monitored as routine AEs.	Removed to ensure consistency across the vedolizumab program.
19.	Section 10.0 Pre-Treatment Events and Adverse Events	A table titled, 'AE Subtypes Defined in This Section' was added.	To comply with EU CTR protocol requirements.
20.	Section 10.2.1.4 AESI Reporting	CCI [redacted]	Revised for consistency across the vedolizumab program.
21.	Section 10.3 Follow-up of SAEs • Subsection 10.3.1 Special Situations Reporting	The subsection on reporting of special situations was added.	To comply with EU CTR protocol requirements.
22.	Section 10.3 Follow-up of SAEs • Subsection 10.3.2 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities	The requirements for suspected unexpected serious adverse reactions reporting were updated.	To comply with EU CTR protocol requirements.

Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
23.	Section 12.3 Sample Retention and Use Section 15.2 Subject Information, Informed Consent, and Subject Authorization • Subsection 15.2.1 Informed Consent for Use of Remaining samples	The details about procedures for collection storage and future use of biological samples were added.	To comply with EU CTR protocol requirements.
24.	Section 2.0 Study Summary Section 3.5 Study Definitions Section 13.1 Statistical and Analytical Plans • Subsection 13.1.3 Safety Analysis	Revised TEAEs definition.	Revised for clarity.
25.	Section 13.1.6 Other Analyses	CCI [redacted]	Ensure consistency across the vedolizumab program.
26.	Section 13.2 Interim Analysis	Revised interim analysis.	Revised to offer more flexibility for interim analyses.
27.	Section 14.2 Protocol Deviations Section 15.3 Subject Confidentiality	The reporting and measures adopted by Takeda in the events of serious data breach were added.	To comply with EU CTR protocol requirements.
28.	Appendix A Schedule of Study Procedures	The weekly schedule has been extended from week 256 to 600.	Revised to align with Section 9.3.2.
29.	Appendix E Sponsor Responsibilities	Sponsor responsibilities were added.	It was missing in the previous protocol amendments and added to provide clarity on the responsibilities of the sponsor.
30.	Global	Updated “legally acceptable representative” to “legally authorized representative” throughout the protocol.	Consistency and clarification throughout protocol.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** Vedolizumab IV	
Title of Protocol: A Phase 2b, Extension Study to Determine the Long-term Safety of Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn's Disease	**IND No.:** 009125	**EU CT No.:** 2023-507766-35
Study Number: Vedolizumab-2005	**Phase:** 2b	

Study Design:

This is a phase 2b, long-term extension study enrolling male and female subjects with ulcerative colitis (UC) or Crohn's disease (CD) who initiated vedolizumab intravenous (IV) treatment in the phase 2 Study MLN0002-2003 between the ages of 2 and 17 years, inclusive. To enter the extension study, subjects will have completed Study MLN0002-2003 and, at Week 22, achieved clinical response as defined by a reduction of partial Mayo score of ≥2 points and ≥25% from Baseline, or a reduction of the Pediatric Ulcerative Colitis Activity Index (PUCAI) of ≥20 points from Baseline for subjects with UC; or a reduction of the Crohn's Disease Activity Index (CDAI) as defined by a ≥70 point decrease from Baseline or a decrease of Pediatric Crohn's Disease Activity Index (PCDAI) of ≥15 points for subjects with CD. The study will evaluate the long-term safety of vedolizumab administered by IV infusion. The study will also evaluate the effect of long-term vedolizumab IV treatment on the time to major inflammatory bowel disease (IBD)-related events (hospitalizations, surgeries, or procedures), health-related quality-of-life measurements, patterns of growth and development, CCI [redacted].

Assessment of eligibility for Vedolizumab-2005 will be determined and informed consent/pediatric assent will be obtained on or after Week 14 through Week 22 of Study MLN0002-2003 based on the clinical response assessments described above. The relevant assessments from the Week 22 Visits of Study MLN0002-2003 will be used as the baseline assessments for this extension study. Subjects entering Vedolizumab-2005 will remain blinded to their dose and will be administered vedolizumab IV once every 8 weeks (Q8W) at the dose administered at Week 14 in Study MLN0002-2003. Blinding of both subject and investigator will continue through week 32 of the Vedolizumab-2005 study. If the subject experiences disease worsening, they may be eligible for dose escalation for subjects on the low-dose of the appropriate weight group. If the subject is receiving the high dose for the appropriate weight group they will not be eligible for dose escalation and will be discontinued from treatment.

CCI [redacted] Subjects who experience disease worsening at any time during Vedolizumab-2005 while receiving the low dose may be escalated to the high dose by satisfying criteria for disease worsening defined by elevations in their clinical assessments (PUCAI for UC patients; and PCDAI for CD patients). Subject dosing will be unblinded at the Week 40 visit so that all Week 32 visit procedures are conducted in a double-blind fashion for analysis purposes. After completion of the MLN0002-2003 study, subjects who have their dose increased based on nonresponse should be dosed based on weight at the time of nonresponse during the Vedolizumab-2005 study. CCI [redacted] The study will include an 18-week follow-up period (final safety visit) and a long-term follow-up safety survey 6 months after the subject's last dose of study drug, for all subjects including those who discontinue the study.

Primary Objective: To determine the safety profile of long-term vedolizumab IV treatment in pediatric subjects with UC or CD.

Secondary Objectives:

- To evaluate the efficacy of long-term vedolizumab IV in pediatric subjects with UC or CD.
- To determine the effect of long-term vedolizumab IV treatment on time to major IBD-related events (hospitalizations, surgeries, and procedures) in pediatric subjects with UC or CD.
- To examine the effect of long-term vedolizumab IV treatment on health-related quality-of- life measurements in pediatric subjects with UC or CD.
- To determine the effect of long-term vedolizumab IV treatment on patterns of growth and development in pediatric subjects with UC or CD.

Subject Population: Male and female pediatric subjects with UC or CD who completed Study MLN0002-2003.

Number of Subjects: Up to 80 rollover subjects from Study MLN0002-2003	**Number of Sites**: Approximately 72 sites in North America, Europe, and the Middle East
Dose Levels: Subjects who weigh ≥30 kg will receive vedolizumab IV 300 mg (high dose) or 150 mg (low dose) Q8W. Subjects who weigh <30 kg will receive vedolizumab IV 200 mg (high dose) or 100 mg (low dose) Q8W.	**Route of Administration**: IV
Duration of Treatment: It is anticipated that the duration of vedolizumab IV treatment will vary by subject on the basis of continued benefit but will be until vedolizumab IV is commercially available for pediatric indication(s) in the subject's country or until other drug access programs become available (whichever comes first), the subject turns 18 years of age and can be transitioned to commercial drug, the subject withdraws from the study, or the sponsor decides to close the study.	**Period of Evaluation:** The first dose of vedolizumab IV in this extension study will be at the Week 22 Visit of Study MLN0002-2003 (or up to 1 week after). All subjects will have an 18-week follow-up period starting from their last dose of study drug and a long-term follow-up safety survey 6 months after their last dose of study drug.

Potential Risks and Benefits

The study will evaluate long-term safety of vedolizumab IV as maintenance therapy in pediatric subjects with moderately to severely active UC or CD who achieved clinical response following vedolizumab IV induction therapy. Vedolizumab IV may provide an alternative therapy and address the unmet medical need in pediatric patients who do not respond or who lose response to all existing therapies (including conventional therapy or TNF-α antagonists), or in whom side effects of these agents are intolerable or life threatening.

Vedolizumab IV demonstrated clinically relevant efficacy in multiple completed clinical studies in adult subjects with moderately to severely active UC or CD. Similar clinical responses were observed in pediatric subjects with UC or CD in Study MLN0002-2003, as those seen in adults in previous phase 3 studies of vedolizumab IV induction therapy.

In clinical studies, vedolizumab has shown an acceptable and consistent safety profile in adult subjects (≥18 years of age) with body weights ranging from 28.7 to 170 kg. In the pivotal phase 3 studies (C13006 and C13007), the most common (≥5% and at a higher incidence than placebo) adverse reactions in subjects administered vedolizumab 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 mucosal addressin cell adhesion molecule-1 (MAdCAM-1) binding sites. No additive risk of infection was identified among subjects who received a concomitant immunosuppressant.

The safety of vedolizumab has been well characterized and the overall safety profile observed in pediatric Study MLN0002-2003 was consistent with the profile seen in adult subjects who received vedolizumab IV. Thus, on the basis of available clinical and postmarketing data, the benefit-risk profile in pediatric subjects with UC or CD is expected to be positive. Further information on vedolizumab is provided in the current edition of the Investigator's Brochure.

Main Criteria for Inclusion:

- The subject is male or female with UC or CD and was between 2 to 17 years, inclusive, at the time of their randomization for Study MLN0002-2003. (Note: A subject remains eligible to participate in this study after they reach 18 years of age if they continue to meet the inclusion criteria and do not meet any exclusion criteria.)
- The subject completed Study MLN0002-2003 and, at Week 22, 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 PCDAI of ≥15 points for subjects with CD.
- The subject may be receiving a therapeutic dose of the following drugs:
  - Oral 5-aminosalicylic (5-ASA) compounds.
  - Oral corticosteroid therapy (prednisone or equivalent steroid at a dose ≤50 mg/day) provided the subject was receiving this medication during prior participation in MLN0002-2003.
  - Topical (rectal) treatment with 5-ASA or corticosteroids.
  - Probiotics (eg, *Saccharomyces boulardii*).
  - Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea.
  - Antibiotics used for treatment of CD (eg, ciprofloxacin, metronidazole).
  - Azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) provided the subject was receiving this medication during prior participation in Study MLN0002-2003.

Main Criteria for Exclusion:

- The subject is female and is lactating or pregnant.
- The subject has hypersensitivity or allergies to vedolizumab or any of its excipients.
- The subject has withdrawn from Study MLN0002-2003.
- The subject has developed any new unstable or uncontrolled cardiovascular, heart failure moderate to severe (New York Class Association III or IV), pulmonary, hepatic, renal, gastrointestinal, 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.
- 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 major surgical intervention for UC or CD (eg, bowel resection), or is anticipated to require major surgical intervention for UC or CD during the study.
- The subject has other serious comorbidities that will limit their ability to complete the study.

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is percentage of subjects with treatment-emergent adverse events (TEAEs).

The secondary endpoints for this study are:

- Percentage of UC subjects who, at Week 32, achieve and maintain clinical response based on complete Mayo score, as defined by a continued reduction in complete Mayo score of ≥3 points from the baseline (at initiation of MLN0002-2003) and continued decrease in rectal bleeding subscore of ≥1 point from baseline, or absolute rectal bleeding subscore of ≤1 point at Week 32.
- Percentage of CD subjects who, at Week 32, achieve and maintain clinical response as defined by a 50% reduction in SES-CD score on endoscopy compared to the baseline endoscopy (at initiation of MLN0002-2003); and continued reduction in CDAI that is a ≥70 point decrease from the baseline CDAI score at the initiation of MLN0002-2003.
- Time to major IBD-related events (hospitalizations, surgeries, or procedures).
- Changes from Baseline in IMPACT-III (where translations are available) total and subscale scores at Week 24 and every 24 weeks, thereafter.
- Height velocity at Week 48 and every 48 weeks, thereafter.
- Change from Baseline in height, weight, and body mass index (BMI) at Week 24 and every 24 weeks, thereafter.
- Percentage of subjects achieving Tanner stage V at or before age 16 years (females) or 17 years (males).

Statistical Considerations:

Treatment-emergent AEs (TEAEs) are undesirable events not present prior to medical treatment or an already-present event that worsens either in intensity or frequency following the treatment, occurring from the first dose of study drug to the day of last dose of study drug + 126 days (accounting for 5 times the half-life of vedolizumab). The number and percentage of subjects with TEAEs (defined as any TEAE, regardless of relationship to study drug), CCI [redacted], AEs leading to discontinuation, and serious AEs 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 Medical Dictionary for Regulatory Activities system organ class, high level term, and preferred term. TEAEs will also be summarized by severity and by relationship to study drug. Separate summaries will be generated for treatment-related AEs overall and by severity. Exposure-adjusted incidence rates will also be analyzed.

The percentage of subjects in clinical response at Week 32 will be summarized.

Time to major IBD-related events (hospitalizations, surgeries, and procedures) will be analyzed and Kaplan-Meier estimates presented every 48 weeks.

Change from Baseline in IMPACT-III total and subscale scores, height, CCI [redacted], weight, and BMI will be summarized descriptively. Height velocity will be summarized by visit. The percentage of subjects achieving Tanner stage V at or before age 16 years (females) or 17 years (males) will be summarized.

Sample Size Justification:

Due to no hypothesis testing, there were no formal sample size calculations done for this study. It is estimated that up to 80 subjects (40 with UC and 40 with CD) who have completed Study MLN0002-2003 will enter this study.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

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

Investigators and subinvestigators will provide the sponsor with sufficient accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

The sponsor will perform all study-related activities with the exception of those identified in the Clinical Study Supplier form. The vendors identified in the form for specific study-related activities will perform those activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

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

3.3 List of Abbreviations

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
CCI	[redacted]
AZA	azathioprine
BMI	body mass index
bpm	beats per minute
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
C difficile	*Clostridium difficile*
CFR	Code of Federal Regulations
CL_L	linear total clearance
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CRF	case report form
CCI	[redacted]
CTR	Clinical Trial Regulation
C_{trough}	serum concentration at the end of a dosing interval
ECG	electrocardiogram
eCRF	electronic case report form
ESR	erythrocyte sedimentation rate
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GI	gastrointestinal(ly)
hCG	human chorionic gonadotropin
IAC	Independent Adjudication Committee
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee

Term	Definition
INR	international normalized ratio
IRB	institutional review board
IRT	interactive web response technology
IV	intravenous(ly)
LFT	liver function test
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
PUCAI	Pediatric Ulcerative Colitis Activity Index
Q4W	once every 4 weeks
Q8W	once every 8 weeks
SAE	serious adverse event
SES-CD	simple endoscopic score for Crohn's disease
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TNF-α	tumor necrosis factor-alpha
TYSABRI	natalizumab
UC	ulcerative colitis
ULN	upper limit of normal
Vedolizumab IV	also known as ENTYVIO; KYNTELES
WBC	white blood cell

3.4 Corporate Identification

TDC Americas	Takeda Development Center Americas, Inc.

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 Study MLN0002-2003 Baseline (or a partial Mayo score of ≥2 points and ≥25% from Study MLN0002-2003 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.
CCI [redacted]	[redacted]
Clinical response based on PUCAI	A ≥20-point decrease from Study MLN0002-2003 Baseline in Pediatric Ulcerative Colitis Activity Index (PUCAI) score.
CCI [redacted]	[redacted]
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 Study MLN0002-2003 Baseline in Crohn's Disease Activity Index (CDAI) score.
CCI [redacted]	[redacted]
Clinical response based on PCDAI	A ≥15-point decrease from Study MLN0002-2003 Baseline in Pediatric Crohn's Disease Activity Index (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 Study MLN0002-2003 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.
CCI [redacted]	[redacted]
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.
Treatment-emergent AEs (TEAEs)	TEAEs are undesirable events not present prior to medical treatment or an already-present event that worsens either in intensity or frequency following the treatment, occurring from the first dose of study drug to the day of last dose of study drug + 126 days (accounting for 5 times the half-life of vedolizumab).
All Subjects:	
Continued disease worsening after a dose escalation	No reduction in the elevated PCDAI or PUCAI scores when next assessed after the increased dose has been administered.
Study start	Defined as the date of the first subject screened in this study.
End of study	The end of study is defined as last subject, last visit (inclusive of the 18-weeks post–last-dose follow-up safety visit).

Term	Definition
Enrollment	Subject is defined as enrolled when all of the following have occurred: • Subject/subject's legally authorized representative or adult caregiver has provided informed consent (that is, in writing, documented via a signed and dated informed consent form). • Subject has provided assent to participate in the study, as required by local regulations. • Subject has completed screening, meeting all eligibility criteria. • Subject takes part in any study activity after screening.

4.0 INTRODUCTION

4.1 Background

4.1.1 Epidemiology of Ulcerative Colitis and Crohn's Disease in the Pediatric Population

The overall prevalence of ulcerative colitis (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 (Loftus 2004; Molodecky et al. 2012; Shivananda et al. 1996; Trallori et al. 1996). 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 (Kappelman et al. 2013). 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 (da Silva et al. 2014). No significant differences in prevalence by sex have been reported for pediatric UC (Kappelman et al. 2013). However, a family history of UC does not seem to be a negative prognostic factor in UC patients (da Silva et al. 2014).

In the United States, the overall prevalence of Crohn's disease (CD) is approximately 125 cases/100,000 of the population and 150 cases/100,000 in Western Europe (Loftus 2004; Shivananda et al. 1996; Trallori et al. 1996). 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 (Kappelman et al. 2013), while a female preponderance is seen only among patients diagnosed during adolescence (13 to 19 years) (Nieuwenhuis and Escher 2008).

A large study in the United States demonstrated that UC, CD, and indeterminate colitis (otherwise known as inflammatory bowel disease unclassified) 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 (Heyman et al. 2005). 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 (Nieuwenhuis and Escher 2008).

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 (Benchimol et al. 2011; Turunen et al. 2006). 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 ages 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%) (IBD Working Group of the European Society for Paediatric Gastroenterology and Nutrition 2005). 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 (Kugathasan et al. 2003). 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 not be sufficient to establish the diagnosis in the pediatric population (Nieuwenhuis and Escher 2008).

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 (Higuchi and Bousvaros 2004). Whether the course differs in children, adolescents, and adults is unknown at present (Nieuwenhuis and Escher 2008). 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 (Amre et al. 2006) 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 (Motil et al. 1993). 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 acids (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 (Prefontaine et al. 2009) and also in moderate to severe pediatric UC (Kader et al. 1999). 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 (Chande et al. 2007; El-Matary et al. 2009; Weiss et al. 2009). 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 (EU), and adalimumab is approved in the United States and EU for moderately to severely active CD (Abbvie 2017).

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 (Briskin et al. 1997; Butcher et al. 1999; Erle et al. 1994; Salmi and Jalkanen 2005). As a result, vedolizumab impairs the migration of gut-homing leukocytes into GI mucosa (Soler et al. 2009) 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) has been granted marketing approval in more than 70 countries, including the United States and EU, 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 SC. 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 after a single dose of vedolizumab 300 mg IV by 30-minute infusion.

A 13-week toxicity study (20063753) of vedolizumab IV in juvenile cynomolgus monkeys (11 to 15 months old at study start) supports studies in the pediatric population (down to 2 years of age). 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. 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

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. Following IV infusion, vedolizumab serum concentrations generally fell in a biexponential fashion until approximately 1 to 10 µg/mL, with a clearance of approximately 0.157 L/day and a serum half-life of around 25 days. Thereafter, the serum concentrations fell in a nonlinear fashion. The volume of distribution for vedolizumab IV is approximately 5 L.

Vedolizumab IV has demonstrated clinically relevant efficacy 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 (Feagan et al. 2013). 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 (Sandborn et al. 2013). 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 (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 intention-to-treat population was not met; however, a treatment difference was observed at Week 10 in this population (Sands et al. 2014). Similar treatment differences favoring vedolizumab were also demonstrated for the overall population and in the subgroup of subjects who were TNF-α antagonist naïve.

In the pivotal phase 3 studies (Studies C13006, C13007, and C13011), 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. Overall, the safety data from long-term treatment with vedolizumab IV Q4W or Q8W in Study C13008 for up to approximately 8 years was consistent with the known safety profile of vedolizumab. 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.

Completed phase 2 pediatric vedolizumab IV Study MLN0002-2003 evaluated treatment with vedolizumab IV through Week 14. Treatment with 150 and 300 mg IV doses (≥30 kg weight group) and 100 and 200 mg IV doses (<30 kg cohort) in pediatric subjects with either UC or CD resulted in similar clinical responses in children compared with those seen in adults in previous phase 3 studies of vedolizumab induction therapy. The overall safety profile observed in pediatric Study MLN0002-2003 was consistent with the profile seen in adult subjects who

received vedolizumab IV. The most common adverse events (AEs) in subjects ≥30 kg were headache and worsening UC or CD. The most common AEs in subjects <30 kg were abdominal pain, anaemia, and worsening CD. SAEs in both weight groups were predominantly worsening UC or CD. There were no new safety signals identified from the study. Vedolizumab was generally safe when administered either as 150 and 300 mg in subjects ≥30 kg or as 100 mg and 200 mg in subjects <30 kg with a comparable safety profile in both weight groups.

Vedolizumab has been marketed for more than 8 years and is approved in more than 70 countries. The safety of vedolizumab has been well-characterized.

The most commonly reported AEs, other than off-label use and product use issues, were exacerbations/complications related to underlying CD and UC. The safety profile in the pediatric population was consistent with that observed in the adult population.

Overall, vedolizumab has been well tolerated in clinical studies and postmarketing experience. The benefit-risk profile continues to be positive.

4.2 Rationale for the Proposed Study

This extension study is intended to characterize the long-term safety profile of vedolizumab IV treatment in pediatric subjects with UC or CD who initiated treatment aged 2 to 17 years at the time of randomization in Study MLN0002-2003, [redacted] and the correlation of the exposure to the drug with the clinical response. To enter the extension study, subjects will have completed Study MLN0002-2003 and, at Week 22, 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 PCDAI of ≥15 points for subjects with CD. Establishing the long-term safety and tolerability of vedolizumab IV treatment in pediatric subjects with UC and CD is essential to understanding the benefit/risk profile in this population. Data regarding the maintenance of clinical response long-term and the occurrence of important clinical events resulting from chronic vedolizumab IV administration in pediatric subjects will be obtained from this extension study.

4.3 Benefit/Risk Assessment

There remains an unmet medical need in pediatric patients who fail to respond or who lose response to all existing therapies (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 demonstrated clinically relevant efficacy in multiple completed clinical studies in adult subjects with moderately to severely active UC or CD. In Study MLN0002-2003, similar clinical responses were observed in pediatric subjects with UC or CD, as compared with those seen in adults in previous phase 3 studies of vedolizumab IV induction therapy.

In clinical studies, vedolizumab has shown an acceptable and consistent safety profile in adult subjects (≥18 years of age) with body weights ranging from 28.7 to 170 kg. In the pivotal phase 3 studies (C13006 and C13007), the most common (≥5% and at a higher incidence than placebo) adverse reactions in subjects administered vedolizumab 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.

The safety of vedolizumab has been well characterized and the overall safety profile observed in pediatric Study MLN0002-2003 was consistent with the profile seen in adult subjects who received vedolizumab IV. Thus, on the basis of available clinical and postmarketing data, the benefit-risk profile in pediatric subjects with UC or CD is expected to be positive. Further information on vedolizumab is provided in the current edition of the Investigator's Brochure.

4.4 Risks Associated With Study Procedures

Subjects may experience discomfort and risks from some study procedures. These include:

- Risks associated with infusion such as infusion site reactions.
- Risks associated with endoscopy such as bleeding, abdominal pain or bloating, perforation.
- Risks associated with general anesthetic during endoscopy such as nausea and vomiting, drowsiness, or confusion.

Subjects will be monitored carefully for these risks. The principal investigator and medical team can implement mitigations to decrease the risk of these events and will also be prepared to treat any issues as needed.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To determine the safety profile of long-term vedolizumab IV treatment in pediatric subjects with UC or CD.

5.1.2 Secondary Objectives

- To evaluate the efficacy of long-term vedolizumab IV in pediatric subjects with UC or CD.
- To determine the effect of long-term vedolizumab IV treatment on time to major IBD-related events (hospitalizations, surgeries, and procedures) in pediatric subjects with UC or CD.

- To examine the effect of long-term vedolizumab IV treatment on health-related quality-of-life measurements in pediatric subjects with UC or CD.
- To determine the effect of long-term vedolizumab IV treatment on patterns of growth and development in pediatric subjects with UC or CD.

5.1.3 Additional Objectives

- CCI

5.2 Endpoints

5.2.1 Primary Endpoint

- Percentage of subjects with treatment-emergent adverse events (TEAEs).

5.2.2 Secondary Endpoints

- Percentage of UC subjects who, at Week 32, achieve and maintain clinical response based on complete Mayo score, as defined by a continued reduction in complete Mayo score of ≥3 points from the baseline (at initiation of MLN0002-2003) and continued decrease in rectal bleeding subscore of ≥1 point from baseline, or absolute rectal bleeding subscore of ≤1 point at Week 32.
- Percentage of CD subjects who, at Week 32, achieve and maintain clinical response as defined by a 50% reduction in SES-CD score on endoscopy compared to the baseline endoscopy (at initiation of MLN0002-2003); and continued reduction in CDAI that is a ≥70 point decrease from the baseline CDAI score at the initiation of MLN0002-2003.
- Time to major IBD-related events (hospitalizations, surgeries, or procedures).
- Changes from Baseline in IMPACT-III (where translations are available) total and subscale scores at Week 24 and every 24 weeks, thereafter.
- Height velocity at Week 48 and every 48 weeks, thereafter.
- Change from Baseline in height, weight, and body mass index (BMI) at Week 24 and every 24 weeks, thereafter.
- Percentage of subjects achieving Tanner stage V at or before age 16 years (females) or 17 years (males).

5.2.3 Additional Endpoints

CCI

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

Study Vedolizumab-2005 is a phase 2b, extension study to determine the long-term safety of vedolizumab IV in pediatric subjects with UC or CD who initiated vedolizumab treatment at 2 to 17 years of age, inclusive, in Study MLN0002-2003 (a phase 2, dose-ranging study). Up to 80 pediatric subjects who completed Study MLN0002-2003 and, at Week 22, 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 PCDAI of ≥15 points for subjects with CD will be enrolled in the study. The study will also evaluate the effect of long-term vedolizumab IV treatment on the time to major IBD-related events (hospitalizations, surgeries, or procedures), health-related quality-of-life measurements, patterns of growth and development, CCI [redacted]. Subjects and investigators will remain blinded to the dose being administered through Week 32 of the study. If the subject experiences disease worsening, they may be eligible for dose escalation for subjects on the low-dose of the appropriate weight group. If the subject is receiving the high dose for the appropriate weight group they will not be eligible for dose escalation and will be discontinued from treatment. CCI [redacted] At Week 40 the blind will be lifted. A schematic of the study design is shown in Figure 6.a.

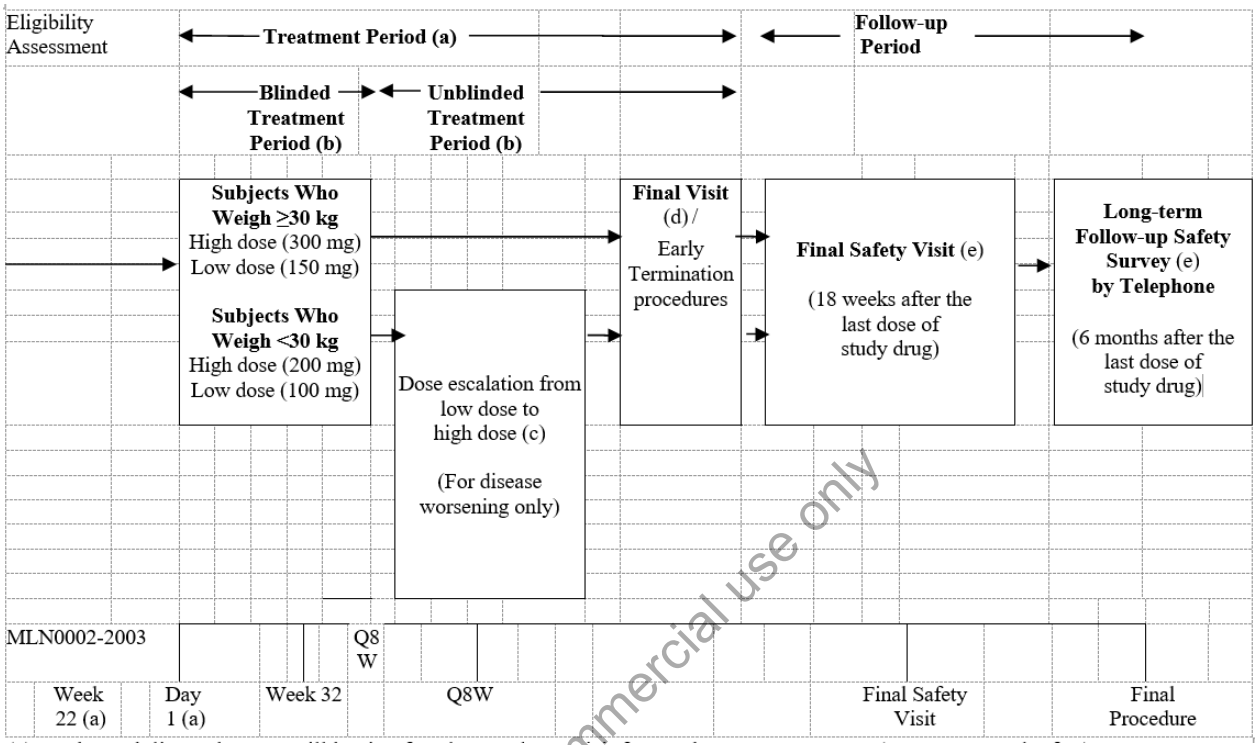
Assessment of eligibility for Vedolizumab-2005 will be determined and informed consent/pediatric assent for participation in Study Vedolizumab-2005 will be obtained on or after Week 14 through Week 22 of Study MLN0002-2003 based on the assessments of clinical response described above. Subjects in MLN002-2003 randomized to the low dose group who have not yet satisfied the criteria for clinical response at Week 14 will undergo a blinded dose escalation to the high dose group and be re-evaluated for clinical response at Week 22 and eligibility to enter Vedolizumab 2005. The relevant clinical assessments from the Week 22 Visits of Study MLN0002-2003 will be used as the baseline assessments for Vedolizumab-2005. The majority of assessments in the extension study will be performed at 8-week intervals or at unscheduled visits when appropriate. CCI [redacted] Safety assessments, CCI [redacted], will be conducted as listed in the Schedule of Study Procedures in Appendix A. It is anticipated that the duration of vedolizumab IV treatment will vary by subject on the basis of continued benefit but will be until vedolizumab IV is commercially available for pediatric indication(s) in the subject's country or until other drug access programs become available (whichever comes first), the subject turns 18 years of age and can be transitioned to commercial drug, the subject withdraws from the study, or the sponsor decides to close the study. The subjects will attend a Final Safety Visit 18 weeks after the last dose of vedolizumab in Study Vedolizumab-2005. The end of study will be when the last subject completes their final safety visit 18 weeks after their last treatment in Study Vedolizumab-2005. During the safety follow-up period, if subjects transition to vedolizumab other than study drug, safety data will be collected until the 18-week safety follow-up visit (eg, 18 weeks after the last dose of study drug). Additionally, subjects will be required to participate in a long-term follow-up safety survey by telephone, 6 months after their last dose of vedolizumab study drug.

Subjects will receive their first dose of vedolizumab IV in this study on Day 1, within 1 week of the MLN0002-2003 Week 22 assessments. At study entry, subjects will be administered the same blinded dose of vedolizumab IV that was received at Week 14 in Study MLN0002-2003 and will then continue to receive vedolizumab IV at a frequency of Q8W. The dosing algorithms for the high dose and low dose groups are summarized in Figure 6.b and Figure 6.c, respectively.

Subjects receiving the low dose (150 or 100 mg) of vedolizumab IV may be escalated to the high dose (300 or 200 mg) at any time during Vedolizumab-2005 if the subject demonstrates disease worsening by PUCAI/PCDAI (Section 3.5) at 2 consecutive visits (scheduled or unscheduled) (Figure 6.c). For UC subjects, disease worsening is defined as 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. For CD subjects, disease worsening is defined as 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.

No further dose escalation will be permitted beyond the high dose per weight category (300 or 200 mg) Q8W. Subjects who experience continued disease worsening during the extension study despite being administered the high dose of vedolizumab Q8W (300 or 200 mg) will be discontinued from the study. Continued disease worsening after a dose escalation is defined as no reduction in the elevated PCDAI or PUCAI scores when next assessed after the increased dose has been administered. After completion of the MLN0002-2003 study, subjects who have entered the Vedolizumab-2005 study and who qualify for a dose increase because of disease worsening will have their dose increased to the maximum allowable dose in the cohort determined by their weight at the time of non-response during the Vedolozumab-2005 study.

Figure 6.a Schematic of Vedolizumab-2005 Study Design



(a) Study Vedolizumab-2005 will begin after the Week 22 Visit for Study MLN0002-2003 (or up to 1 week after). Subjects who consent to participate in the extension study (Vedolizumab-2005) may continue blinded study dosing after MLN0002-2003 Week 22 End-of-Study Visit procedures have been completed.

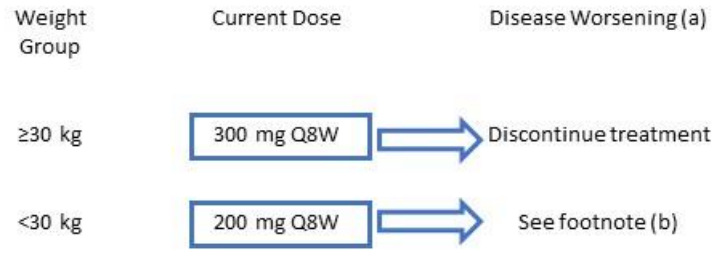
(b) Subjects will continue blinded study dosing through Week 32 of Study Vedolizumab-2005. If the subject experiences disease worsening, they may be eligible for dose escalation for subjects on the low-dose of the appropriate weight group. If the subject is receiving the high dose for the appropriate weight group they will not be eligible for dose escalation and will be discontinued from treatment. The dose will be unblinded at Week 40.

(c) If a subject demonstrates disease worsening by PUCAI/PCDAI (Section 3.5) at 2 consecutive visits (scheduled or unscheduled) they may be eligible for dose escalation. This information will be entered into IRT. Subjects eligible for a dose escalation will be dosed based on their weight at the time of nonresponse in Study Vedolizumab-2005. Subjects who were on the high dose for their current weight group will not be eligible for a dose escalation and will be discontinued from treatment. Subjects who show continued disease worsening despite dose escalation will be discontinued from the study. Continued disease worsening after a dose escalation is defined as no reduction in the elevated PCDAI or PUCAI scores when next assessed after the increased dose has been administered.

(d) Duration of vedolizumab IV treatment will vary by subject on the basis of continued benefit but will be until vedolizumab IV is commercially available for pediatric indication(s) in the subject's country or until other drug access programs become available (whichever comes first), the subject turns 18 years of age and can be transitioned to commercial drug, the subject withdraws from the study, or the sponsor decides to close the study.

(e) Subjects will complete 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 the last dose of study drug.

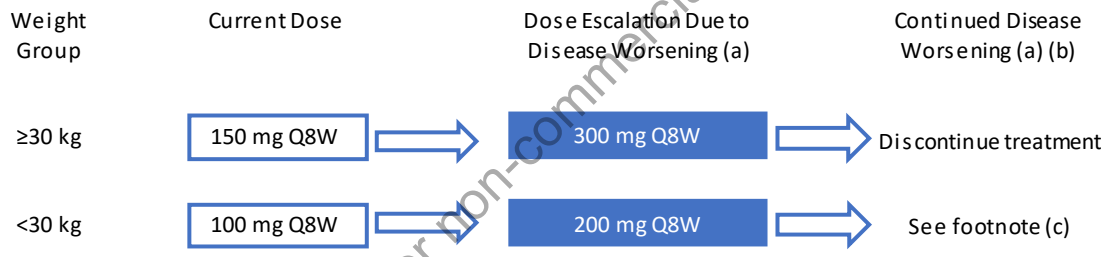
Figure 6.b Schematic of Dosing Algorithm for Subjects in High Dose Groups in Open-label Period



(a) Definition of disease worsening: For UC, 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. For CD, 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.

(b) Subjects who have their dose increased based on nonresponse should be dosed based on weight at the time of nonresponse. If subjects' weight has remained <30 kg at time of nonresponse, discontinue treatment. If subjects' weight has increased to ≥30 kg at time of nonresponse, increase dose to 300 mg Q8W.

Figure 6.c Schematic of Dosing Algorithm for Subjects in Low Dose Groups in Open-label Period



(a) Definition of disease worsening: For UC, 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. For CD, 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.

(b) Continued disease worsening after a dose escalation is defined as no reduction in the elevated PCDAI or PUCAI scores 8 weeks after the increased dose has been administered.

(c) Subjects who have their dose increased based on nonresponse should be dosed based on weight at the time of nonresponse. If subjects' weight has remained <30 kg at time of nonresponse, dose will increase to 200 mg Q8W. If subjects' weight has increased to ≥30 kg at time of nonresponse, dose will increase to 300 mg Q8W.

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Justification for Study Design and Endpoints

This study is intended to gather data on the long-term safety of vedolizumab IV treatment in eligible pediatric subjects who have completed Study MLN0002-2003. In this extension study of maintenance therapy for subjects who have responded to induction therapy, subjects will receive their first dose of study drug within 1 week of the MLN0002-2003 Week 22 assessments. It is anticipated that the duration of vedolizumab IV treatment will vary by subject on the basis of continued benefit but will be until vedolizumab IV is commercially available for pediatric indication(s) in the subject's country or until other drug access programs become available (whichever comes first), the subject turns 18 years of age and can be transitioned to commercial drug, the subject withdraws from the study, or the sponsor decides to close the study.

Safety evaluations will be based on the incidence, severity, and type of TEAEs (including clinically significant changes or abnormalities in the subject's physical examinations), CCI [redacted]

The study will also evaluate the effect of long-term vedolizumab treatment on the time to major IBD-related events (hospitalizations, surgeries, or procedures), health-related quality-of-life measurements, and patterns of growth and development, to characterize the benefit/risk profile in pediatric subjects.

CCI [redacted]

6.2.2 Dose Justification

The approved initial dose and administration regimen of vedolizumab IV in adult subjects is 300 mg administered at Day 1 and Weeks 2, 6, and Q8W thereafter. The dose regimen for pediatric subjects in this extension study is 300 or 150 mg (for subjects who weigh ≥30 kg) or 200 or 100 mg (for subjects who weigh <30 kg) vedolizumab IV Q8W.

Vedolizumab PK and exposure-response have not yet been established in pediatric subjects. C_{trough} values at steady state for vedolizumab doses of 300, 200, 150, and 100 mg administered Q8W or Q4W were simulated using a population PK model developed from data from phase 3 studies 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, 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. Body weights in the adult pivotal phase 3 studies ranged from 28.7 to 170 kg; therefore, body weights ≥30 kg were represented in the adult population. No clinically meaningful differences in safety were observed in adult subjects across quartiles of body weights.

The vedolizumab IV Q8W dosing regimen selected for the long-term extension study is intended to maintain clinical response at the lowest possible exposure. The doses and dosing regimen selected provide estimated 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.

Subjects receiving the low dose (150 or 100 mg) of vedolizumab IV may be escalated to the high dose (300 or 200 mg) if the subject demonstrates disease worsening by PUCAI/PCDAI (Section 3.5) at 2 consecutive visits (scheduled or unscheduled). No further dose escalation will be permitted over 300 or 200 mg Q8W. Subjects who experience continued disease worsening during the extension study despite being administered vedolizumab 300 or 200 mg Q8W will be discontinued from the study. Continued disease worsening after a dose escalation is defined as no reduction in the elevated PCDAI or PUCAI scores when next assessed after the increased dose has been administered.

Results from a 13-week juvenile monkey toxicity study also showed that vedolizumab was safe and well tolerated at doses up to 100 mg/kg, which was the highest dose tested. Taken together, the nonclinical data in a 13-week toxicity study in juvenile cynomolgus monkeys and the long-term safety data available in adult subjects administered vedolizumab IV support long-term treatment of pediatric subjects with UC or CD, who continue to benefit from the therapy.

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 one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for 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.

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.

In the event that this study is terminated and a subject who has benefited from treatment is not able to obtain vedolizumab commercially, the sponsor would seek to take steps to allow continued access to the drug via an extended access or similar program.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study.

1. In the opinion of the investigator, the subject, 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 is male or female with UC or CD and was 2 to 17 years of age, inclusive, at the time of randomization for Study MLN0002-2003. (Note: A subject remains eligible to participate in this study after they reach 18 years of age if they continue to meet the inclusion criteria and do not meet any exclusion criteria.)
4. The subject completed Study MLN0002-2003 and, at Week 22, 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 PCDAI of ≥15 points for subjects with CD.

5. The subject may be receiving a therapeutic dose of the following drugs:
   a) Oral 5-ASA compounds.
   b) Oral corticosteroid therapy (prednisone or equivalent steroid at a dose ≤50 mg/day) provided the subject was receiving this medication during prior participation in MLN0002-2003.
   c) Topical (rectal) treatment with 5-ASA or corticosteroids.
   d) Probiotics (eg, *Saccharomyces boulardii*).
   e) Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea.
   f) Antibiotics used for the treatment of CD (ie, ciprofloxacin, metronidazole).
   g) AZA or 6-MP or MTX, provided the subject was receiving this medication during prior participation in MLN0002-2003.
6. 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.
7. 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 highly effective methods of contraception are defined in Section 9.1.15 and reporting responsibilities are defined in Section 9.1.16.

8. The subject met inclusion criterion #10 in the MLN0002-2003 protocol (the subject's vaccinations are up to date) prior to enrollment.

7.2 Exclusion Criteria

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

1. The subject is female and is lactating or pregnant.
2. The subject has hypersensitivity or allergies to vedolizumab or any of its excipients.
3. The subject has withdrawn from Study MLN0002-2003.
4. The subject has developed any new 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.

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 major surgical intervention for UC or CD (eg, bowel resection), or is anticipated to require major surgical intervention for UC or CD during the study.
7. 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 first dose of study drug.
8. The subject has other serious comorbidities that will limit his or her ability to complete the study.
9. 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.
10. The subject has history of lupus.
11. The subject is unable to comply with all study assessments.
12. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

7.3 Excluded Medications, Vaccinations, 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 30 days prior to first dose of study drug in Study MLN0002-2003 and for at least 6 months after the last dose of study drug in Study Vedolizumab-2005.
- 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).

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

Subjects who do not respond to treatment or show worsening of their disease after entering the safety follow-up period will no longer need to abstain from the medications that were prohibited during the screening and treatment periods. High dose glucocorticoids and other treatments will be allowed. Biologics or nonbiologic immunosuppressants should not be initiated during the safety follow-up period without prior discussion with the sponsor study physician or designee due to the long half-life of vedolizumab.

7.3.1 Permitted Medications and Treatments for IBD

The following medications and treatments are permitted during the study:

- Immunomodulators (such as MTX, AZA, 6-MP as described in inclusion criterion 5.g).
- Oral 5-ASAs, probiotics, enteral nutrition, or antibiotics.
- Antidiarrheals for control of chronic diarrhea.
- Topical (rectal) treatment with 5-ASAs or corticosteroids.
- These treatments may be initiated at the discretion of the investigator during the long-term maintenance therapy with vedolizumab.

7.3.1.1 Oral Corticosteroid Dosing

Newly initiated corticosteroids are prohibited. If a subject was receiving corticosteroids during their participation in MLN0002-2003, the maximum dose of oral corticosteroids for the treatment of UC or CD that may be coadministered with vedolizumab IV as a long-term regimen is ≤50 mg/day of prednisone (or equivalent steroid). Initiation of tapering of the corticosteroid dose during the Vedolizumab-2005 study is at the discretion of the investigator and should follow a schedule of a reduction of 5 mg each week down to a daily dose of 10 mg/day. Thereafter, the dose may be reduced by 2.5 mg each week until the subject has been weaned off corticosteroids (consult with the medical monitor for support, if needed).

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.

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

- Liver function test (LFT) abnormalities.

  Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.12), if the following circumstances occur at any time during study drug treatment:

  – Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 times the upper limit of normal (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. 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 10.1.3.
   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 authorized 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 9.1.16.
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 their 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, the Final Safety Follow-up Visit and the 6-month long-term follow-up safety survey. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Vedolizumab IV

The sponsor will supply the study sites with the following study drug: vedolizumab IV 300 mg/vial, for single use in a 20 mL vial. The study drug will be provided in a glass vial as a lyophilized solid formulation for reconstitution using sterile water. 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 (protected from light).

Vedolizumab IV must be stored at 2ºC to 8ºC (36ºF to 46ºF) at the site. A daily temperature log of the drug storage area at the site must be maintained. For details regarding study drug storage, handling, and disposal please refer to the pharmacy manual.

8.1.3 Dose and Regimen

Subjects will receive their first dose of study drug in this study on Day 1 (up to 1 week after the MLN0002-2003 Week 22 Visit). Subjects will continue to receive vedolizumab IV at the same dose administered at Week 14 in Study MLN0002-2003, which will be administered at a frequency of Q8W.

Subjects receiving the low dose (150 or 100 mg) vedolizumab IV who demonstrate disease worsening by PUCAI/PCDAI (Section 3.5) at 2 consecutive visits (scheduled or unscheduled) may dose escalate to high dose (300 or 200 mg) vedolizumab IV Q8W (Section 6.2.2). No further dose escalation will be permitted beyond the high dose per weight category (300 or 200 mg) Q8W. Subjects who experience continued disease worsening during the extension study despite being administered high dose vedolizumab Q8W will be discontinued from the study. Continued disease worsening after a dose escalation is defined as no reduction in the elevated PCDAI or PUCAI scores when next assessed after the increased dose has been administered.

The predefined algorithm for determination of dose and dose frequency is summarized in Table 8.a. After completion of the MLN0002-2003 study, subjects who have their dose increased based on nonresponse should be dosed based on weight at the time of nonresponse.

Table 8.a Dose and Regimen

Weight Category (a) **Vedolizumab Dose at Week 14 in Study MLN0002-2003**	**Extension Study (Day 1)**	**Disease Worsening (b)(c)**
≥30 kg		
300 mg (high dose)	300 mg Q8W	Discontinue from study
150 mg (low dose)	150 mg Q8W	Escalate to 300 mg Q8W Discontinue from study for continued disease worsening
<30 kg		
200 mg (high dose)	200 mg Q8W	See footnote (d)
100 mg (low dose)	100 mg Q8W	See footnote (e) Discontinue from study for continued disease worsening

(a) After completion of the MLN0002-2003 study, subjects who have their dose increased based on nonresponse should be dosed based on weight at the time of nonresponse.

(b) For UC, disease worsening is defined as 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. For CD, it is defined as 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.

(c) Continued disease worsening after a dose escalation is defined as no reduction in the elevated PCDAI or PUCAI scores when next assessed after the increased dose has been administered.

(d) If subjects' weight has remained <30 kg at time of nonresponse, discontinue treatment. If subjects' weight has increased to ≥30 kg at time of nonresponse, increase dose to 300 mg Q8W.

(e) If subjects' weight has remained <30 kg at time of nonresponse, increase dose to 200 mg Q8W. If subjects' weight has increased to ≥30 kg at time of nonresponse, increase dose to 300 mg Q8W.

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 1 hour after each infusion.

Duration of vedolizumab IV treatment will vary by subject on the basis of continued benefit but will be until vedolizumab IV is commercially available for pediatric indication(s) in the subject's country or until other drug access programs become available (whichever comes first), the subject turns 18 years of age and can be transitioned to commercial drug, the subject withdraws from the study, or the sponsor decides to close the study.

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, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented according to Section 10.0, Pretreatment Events and Adverse Events.

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

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

8.2 Investigational Drug Assignment and Dispensing Procedures

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

The subject number assigned at Screening in Study MLN0002-2003 will be used in this study. The investigator or investigator's designee will access the interactive web response technology (IRT) system and provide the necessary subject-identifying information. 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, and the medication ID number of the investigational drug to be dispensed will be provided by the IRT.

8.3 Randomization Code Creation and Storage

Treatment assignment is not randomized in this study. However, subjects will retain the subject number assigned in Study MLN0002-2003.

8.4 Investigational Drug Blind Maintenance

The study drug blind will be maintained using the IRT.

The blind will be removed at the Week-40 study visit.

8.5 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.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

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

Assessment of eligibility for Vedolizumab-2005 will be determined and informed consent/pediatric assent will be obtained on or after Week 14 through Week 22 of Study MLN0002-2003.

Informed consent/pediatric assent must be obtained prior to the subject entering into this study, and before any protocol-directed procedures are performed. The unique subject identification number (subject number) assigned to each subject in Study MLN0002-2003 will be used throughout this extension 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

Subject demographic information will be obtained from Study MLN0002-2003 (depending on local regulations) and will include sex, Hispanic ethnicity, race as described by the subject or parent/guardian, and smoking status at Screening. Date of birth or age will be collected for Vedolizumab-2005.

Race and ethnicity data will be collected in this study to understand how similar the enrolled population is to the population with UC or CD at large and to enable researchers understand if the efficacy and/or safety of vedolizumab IV could be different for people of different races or ethnicities.

Medical history and medication history (including prior biologic medication history information) will be obtained from Study MLN0002-2003.

For Vedolizumab-2005, medical history refers to any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent/assent for the

Vedolizumab-2005, and will include ongoing and resolved AEs from Study MLN0002-2003. Ongoing AEs from Study MLN0002-2003 which change in severity will be reported as new AEs in this study (Section 10.2.1). Where possible, all prior medications for the treatment of UC or CD, including date of diagnosis, with the reason for discontinuation, will be imported from the Study MLN0002-2003 data. Some medications for the treatment of UC or CD, other than the study drug vedolizumab, which started and stopped during Study MLN0002-2003 will need to be manually entered into the eCRF at the first visit.

9.1.3 Physical Examination Procedure

The physical examination 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; (11) other. Physical examinations should be conducted prior to dosing, if applicable.

All physical examinations should assess clinically significant changes from the assessment prior to first dose examination in Study MLN0002-2003. A clinically significant finding will be recorded as an AE if it starts after the first dose of study drug in this study.

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 Procedures

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

After consenting/assenting, subjects and parents/legal guardians will be re-instructed on the completion of diary entries during the study.

A minimum of 3 days (UC) or 5 days (CD) of completed daily diary data prior to the Day 1 visit is required for disease activity index calculation. During the rest of the study, 7 days (UC) or 10 days (CD) of completed daily diary data prior to each scheduled visit per the Schedule of Study Procedures (Appendix A) is required for disease activity index calculation. For unscheduled visits due to flares, the subject should start filling out daily diary sheets when the flare begins (if possible) and then come in for the unscheduled visit for evaluation. A flare is confirmed by observing the subject during a one-week interval (to confirm that it is ongoing) and during that

week, the diaries can continue to be filled out to make sure the subject has 7 days of symptom diaries if they have UC and 10 days of symptom diaries if they have CD.

Diary entries will be reviewed by site personnel at Day 1 (prior to dosing, if applicable) and at the visits specified in the Schedule of Study Procedures (Appendix A) and at any unscheduled visit(s) due to disease exacerbation.

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.

9.1.6.1.1 UC Activity

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

A partial Mayo score will be derived at all scheduled visits per the Schedule of Study Procedures (Appendix A) and at any unscheduled visit(s) due to disease exacerbation (see Appendix H). CCI [redacted] Subjects/parents or legal guardians will make daily entries into the diary for 7 days prior to the scheduled visit, which will be used for Mayo score calculation. The symptoms of UC must be recorded throughout the study. 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.

9.1.6.1.2 CD Activity

A CDAI score (see Appendix K) will be evaluated using the subject's/parent's or legal guardian's paper diary entries collected for 10 days prior to the scheduled visit and laboratory results collected at every scheduled visit during the study as per the Schedule of Study Procedures (Appendix A).

A PCDAI score (see Appendix G) will be evaluated according to the Schedule of Study Procedures (see Appendix A).

Efficacy measurements will be made CCI [redacted] at Week 32, CCI [redacted] and at exit based on endoscopy using SES-CD score (see Appendix I) and the CDAI (see Appendix K), CCI [redacted]

CCI [redacted] The CDAI should also be completed at the time of a flare and at times of possible dose escalation.

9.1.7 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 every 24 weeks to subjects aged 9 to 17 years at the time of first dose of study drug for Study Vedolizumab-2005. The current version will be provided in the study manual.

Questionnaire entries will be reviewed by site personnel at appropriate scheduled visits during the study while the subject is present. Any changes should be made directly to the questionnaire source by the subject/parent or legal guardian. Questionnaire entries will be transcribed by site personnel into the eCRF.

9.1.8 Tanner Stage Evaluation

Tanner Stage Evaluation (see Appendix J) is a scale used to evaluate growth parameters standardized for age, sex, and pubertal development (Marshall and Tanner 1970; Marshall and Tanner 1969) and will be performed every 16 weeks as specified in the Schedule of Study Procedures (Appendix A).

9.1.9 Documentation of Concomitant Medications and Procedures

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

At each study visit (from signing of informed consent/assent through the end of the study), subjects or parents/legal guardians will be asked whether the subject has 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.

9.1.10 CCI [redacted]

[redacted]

9.1.11 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.

9.1.12 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood drawn at any single visit is approximately 11.5 mL for subjects who weigh ≥30 kg and approximately 8.5 mL for subjects who weigh <30 kg. The total volume of blood drawn is approximately 58.0 mL for subjects who weigh ≥30 kg and approximately 43.0 mL for subjects who weigh <30 kg over each 12-month period.

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. These tests should be performed as specified in the Schedule of Study Procedures (Appendix 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.

CCI [redacted]

If subjects experience ALT or AST ≥3×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-glutamyl transferase [GGT], and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Please refer to Section 7.5 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 these 2 consecutive occasions the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE. Please refer to Section 10.2.3 (Reporting of Abnormal LFTs) for reporting requirements.

Table 9.a Clinical Laboratory Tests

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

C difficile: *Clostridium difficile*; ESR: erythrocyte sedimentation rate; hCG: human chorionic gonadotropin; RBC: red blood cell.

9.1.13 Fecal Calprotectin Sample Collection

A stool sample will be collected for the analysis of fecal calprotectin, a biomarker of intestinal inflammatory activity as specified in the Schedule of Study Procedures (Appendix A), and at any point in the study when a subject becomes symptomatic, including worsening of disease activity. The stool sample must be collected before any bowel preparation is given for endoscopy.

9.1.14 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 at any point in the study when a patient becomes symptomatic, including worsening of disease activity. The stool sample must be collected before any bowel preparation is given for endoscopy.

9.1.15 Contraception and Pregnancy Avoidance Procedure

9.1.15.1 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.

9.1.15.2 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.**

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

** Sterilized males should be at least 1 year 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 the Study MLN0002-2003 Week 22 Visit, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative urine hCG pregnancy test prior to receiving any dose of study drug (as close as possible and prior to first dose of study drug, preferably on the same day).

9.1.16 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, ET/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.

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

All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed for 1 year after delivery for outcomes of both the mother and child, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.17 CCI

[redacted]

9.1.18 CCI

[redacted]

CCI [redacted]

9.1.19 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:

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

9.1.20 Documentation of Study Entrance

Only subjects who have assented and their caregivers (as applicable) have consented, and who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into this extension study. Some information to confirm entry will be obtained from the MLN0002-2003 Week 22 assessments, which will be used for the pre-enrollment Day 1 Visit of this study. If a subject is found to be not eligible for entry to this study, the investigator should record the primary reason for failure on the applicable eCRF.

9.1.21 Endoscopies

An endoscopy will be performed at Week 32 as part of the clinical assessment. This will involve a flexible sigmoidoscopy (sigmoidoscope) or a colonoscopy, performed with an endoscope following a cleansing preparation (oral or rectal cathartic). The Week 32 endoscopy will be read centrally for the efficacy analysis through the use of video recordings. 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. CCI [redacted]

9.2 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.

9.3 Schedule of Observations and Procedures

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

9.3.1 Randomization

Treatment is not randomly assigned in this study. Subjects will be assigned to the same dose of study drug received at Week 14 of Study MLN0002-2003.

9.3.2 Final Visit or ET

It is anticipated that the duration of vedolizumab treatment will vary by subject on the basis of continued benefit but will be until vedolizumab IV is commercially available for pediatric indication in the subject's country or until other drug access programs become available (whichever comes first), the subject turns 18 years of age and can be transitioned to commercial drug, the subject withdraws from the study, or the sponsor decides to close the study. The final visit is to be completed within 8 weeks following a pre-agreed-upon subject's last dose (determined by the investigator) and prior to any planned dose if the subject is to transition to commercial drug or other drug access program. Subjects are still expected to complete both the final safety follow-up visit (Section 9.3.3), which is performed at 18 weeks post-last dose, and the long-term follow-up safety survey (phone call), which is completed 6 months after the last dose of study drug (Section 9.3.4). The procedures listed in Schedule of Study Procedures (Appendix A) at the Final Visit/ET Visit will be performed and documented.

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

9.3.3 Final Safety Follow-up Visit

The final safety follow-up visit will be performed 18 weeks after the last dose of study drug. Subjects are expected to complete the final safety follow-up visit. The procedures listed in Schedule of Study Procedures (Appendix A) will be performed and documented.

9.3.4 Long-term Follow-up Safety Survey

Upon completion of treatment, or early termination from the study, all subjects will participate in the long-term follow-up safety survey, conducted by telephone 6 months after the last dose of study drug, unless the subject withdraws consent or is lost to follow-up. If the subject continues with treatment outside of the study, the 6-month follow-up by phone call will be based on the last dose of study drug in Study Vedolizumab-2005 (and not based on receipt of commercially available vedolizumab or vedolizumab provided in a drug access program).

9.3.5 Poststudy Care

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.

Posttrial access to commercially available vedolizumab IV may be provided by the sponsor. Continued access to vedolizumab IV for participants will be terminated for those individuals in this study who no longer benefit from the drug, when the benefit-risk no longer favors the individual, if vedolizumab IV becomes available either commercially or via another drug access mechanism, or when an alternative appropriate therapy becomes available. Posttrial access may be terminated in a country or geographical region where marketing authorization has been rejected or the development of vedolizumab IV has been suspended or stopped by the sponsor.

9.3.6 Unscheduled Visits Due to Disease Exacerbation

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

- Physical examination (including weight and height).
- Fistula assessment (subjects with CD only).
- Vital signs assessment.
- Diary review.
- 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 child-bearing potential.
- PUCAI/PCDAI.
- Partial Mayo score.
- [redacted]

[redacted]

There is no minimum time for repeat evaluation by unscheduled visit in order 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).

9.3.7 Other Unscheduled Visits (if Applicable)

Subjects may return to the study center for unscheduled visit as needed. Unscheduled visits can be performed when the subject has a study related issue in between regular visits (ie, 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 9.3.6 should be performed.

9.3.8 Alternative Approaches to Study Procedures and Data Collection Due to a Pandemic

In unavoidable circumstances, in particular a pandemic (eg, COVID-19 or other future similar unexpected public health concern), that impact the study site's ability to conduct study procedures according to the Schedule of Study Procedures (Appendix A), contingency measures may be implemented. In acknowledgement of hospital, local, state, or national government restrictions or other site-related factors caused by unavoidable circumstances (ie, COVID-19 pandemic) that may prevent investigators from conducting the study according to the Schedule of Study Procedures (Appendix A), investigators may seek approval from the medical monitor to continue subjects in the study despite departure from the Schedule of Study Procedures (Appendix A). Any procedures not conducted per the original study plan will be documented in the study records.

Because a pandemic or other major health crisis (eg, COVID-19) may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the principal investigator in consultation with the sponsor or designee, while maintaining subject safety and confidentiality as the priority.

The principal investigator should also notify the IEC/IRB, as appropriate, about any deviation for temporary use of alternative methods for conducting subject visits (eg, video conferencing, telephone visits) in the event of restrictive measures due to a pandemic (eg, COVID-19), per local requirements.

Procedural changes due to COVID-19 (or other similar pandemic) may include the following:

- All attempts should be made to perform the assessments with the subject present at the site using the visit windows. Exceptions may be granted for alternative approaches to study procedures and data collection through approval by the sponsor or designee. Such instances must be documented in the study records and may include the following:
  - Sites impacted by a pandemic (eg, COVID-19) must contact the sponsor or designee to discuss individual subject and site circumstances to obtain approval for use of alternative approaches to study procedures and data collection.
  - Sites may seek approval from the medical monitor for subjects to continue in the study despite departure from the Schedule of Study Procedures (Appendix A). Principal

investigators are expected to evaluate the impact on the safety of the study participants and site personnel for subjects to continue. In evaluating such requests, the sponsor or designee will give the highest priority to the safety and welfare of the subjects. Subjects must be willing and able to continue taking study medication and remain compliant with the protocol.

- Informed consent procedure: If necessary and required locally, informed consent from a study participant may be obtained via verbal consent when these individuals are unable to travel to the site. Informed consent forms will be signed once the subject can return in person to the study site.
- Clinic visits: For clinic visits (other than the final visit/ET visit and the safety follow-up visit), alternative methods for conducting subject visits (eg, telemedicine visits, such as video conferencing or telephone visits,) may be used with prior approval by the sponsor or designee:
  - When approval is given for a clinic visit to be conducted using an alternative approach, a study-site physician will speak directly with the subject by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status.
  - Assessments: During visits using an alternative method, the study-site physician or other qualified site personnel should contact the subject and conduct the following assessments within specified visit window timeframes: AE/SAE collection, documentation of concomitant medication and procedures, diary review, subject assessment of disease activity based on subject-reported symptoms, and patient-reported outcome assessment (IMPACT-III). Sites may record the scores of the IMPACT-III assessments on behalf of the subject, with the subject's agreement, in the event of a telemedicine visit. For subjects with UC, subject-reported components of the partial Mayo score should be recorded in the daily diary per protocol. For all subjects, the investigator's assessment of disease activity should still be performed based on subject-reported symptoms and recorded in the source documents even if a physical examination cannot be performed.
  - Collection of clinical laboratory samples: Safety laboratory assessments (ie, clinical chemistry and hematology) should be conducted at least every 16 weeks. If a subject is unable to visit the study site because of a pandemic (eg, COVID-19), sites may elect to use local laboratories if it is feasible for the subject to visit a local laboratory sooner than the study site for sample collection. Local laboratory assessments should include clinical chemistry and hematology, as specified in Table 9.a, and results should be communicated to the medical monitor and used to ensure subject safety. Stool samples and collection of samples for FSH, fecal calprotectin, CCI [redacted] are not required when local laboratories are used; however, sampling for these assessments will be resumed on the subject's subsequent visit to the site

  - Protocol deviations: Any deviations from the protocol-specified procedures due to a pandemic (eg, COVID-19 or other similar pandemic) will be recorded as related to a pandemic (eg, COVID-19).

- Final visit/ET visit and safety follow-up visit: The final visit/ET visit and the safety follow-up visit should be performed with the subject present at the study site. If the visit cannot be conducted onsite within the visit window, sites may conduct final visit procedures remotely as is feasible, including using local laboratories for assessment of clinical chemistry and hematology (as specified in Table 9.a). Assessments that cannot be completed during the protocol-specified window will be recorded as a protocol deviation, and such deviations will be recorded in the study records as related to a pandemic (eg, COVID-19 or other similar pandemic).
- Discontinuation or withdrawal from the study or study medication: If a subject chooses to withdraw from the study or study medication because of personal concerns related to a pandemic (eg, COVID-19), this must be specified as the reason for subject withdrawal in the eCRF.

For subjects who are impacted, any alternative approaches to study procedures (ie, procedures not conducted per the Schedule of Study Procedures [Appendix A]) due to a pandemic (eg, COVID-19 or other similar pandemic) must be documented in the study records as related to a pandemic (eg, COVID-19). Data collected using alternative methods may be handled differently in the final data analyses. This will be documented in the statistical analysis plan.

10.0 PRE-TREATMENT EVENTS AND ADVERSE EVENTS

Table 10.a AE Subtypes Defined in This Section

Safety Event	How to Reports Event to Safety	Reporting Timelines to Sponsor
SAEs/AESIs	• Complete AE eCRF (If EDC is down, submit paper SAE form)	Within 24 hours of awareness
Pregnancy	• Complete and submit paper pregnancy form	24 hours
SSRs	• Complete and submit paper SSR form	7 days

AE: adverse event; AESI: adverse event of special interest; eCRF: electronic case report form; EDC: electronic data capture; SAE: serious adverse event; SSR: special situation reporting.

10.1 Definitions

10.1.1 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.

10.1.2 Additional Points to Consider for 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 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.
- AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as an 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 an AE(s).

Laboratory values:

- Changes in laboratory values are only considered to be 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 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 AEs. Baseline evaluations (eg, laboratory tests) should NOT be recorded as AEs 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 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 an 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 an 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 AEs:

- If the subject experiences a worsening or complication of an AE (from MLN0002-2003) after first administration of the study drug in Vedolizumab-2005, 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:

- If the subject experiences changes in severity of an AE, 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 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 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 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 AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.3 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.b).

Table 10.b Takeda Medically Significant AE List

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

10.1.4 AESIs

An AESI (serious or nonserious) is an event of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them. CCI [redacted]

10.1.5 Severity of 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.

10.1.6 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 can be argued, 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.

10.1.7 Relationship to Study Procedures

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

10.1.8 Start Date

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

10.1.9 Stop Date

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

10.1.10 Frequency

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

10.1.11 Action Concerning Study Drug

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

- Dose 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.

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by one 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 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 state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE 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 AE Collection Period

Collection of AEs will commence from the time the subject is administered study drug in this study. Pretreatment events and AEs in the prior study (MLN0002-2003) will be considered Medical History in this study (Section 9.1.2).

Routine collection of AEs will continue until the safety follow-up visit which is 18 weeks after the last dose of study drug.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

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 AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

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

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

10.2.1.4 AESI Reporting

If an AESI occurs during the treatment period or the follow-up period and is considered to be clinically significant based on the criteria below, it should be recorded in the AESI 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.

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[redacted]

CCI [redacted]

10.2.2 Collection and Reporting of SAEs

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

A Takeda SAE eCRF or 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.

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, follow-up of additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed should be reported appropriately.

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 9.1.12 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 Special Situations Reporting

For vedolizumab, pregnancies, and uses not foreseen in the protocol (abuse, misuse, medication error, overdose, or other) are subject to the same reporting obligations as adverse drug reactions. Any special situation event should be reported to the Pharmacovigilance database using a separate paper-based form. Pregnancies are to be reported within 24 hours, with all other special situations to be reported within 7 calendar days.

10.3.2 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 and Eudravigilance database, according to EU Regulation No. 536/2014, as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the 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 COMMITTEE

11.1 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.

12.0 DATA HANDLING AND RECORD KEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, 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 (WHODrug).

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 during the conduct 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 on the eCRFs.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study the 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 forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent/assent 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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents 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.

12.3 Sample Retention and Use

Serum samples collected as part of the study will be stored and may be used for future research purposes up to 15 years after the date of study completion. Samples will be destroyed by a third party vendor per company standard operating procedures. Samples will be stored according to the laboratory manual. If a participant withdraws consent for future use of samples, the investigator must inform the sponsor immediately and the samples will be discarded following the local procedure (ie, where the sample resides at the time of withdrawal). The tests performed with these samples are not intended to make determinations about a participant's health or the likelihood that a participant will develop any disease, so no test results will be provided to the investigator or put into a participant's medical record. Test results should not be discussed with a participant unless required by local law.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

The statistical analysis plan will be finalized prior to the first interim analysis. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Data will be analyzed by indication.

13.1.1 Analysis Sets

The full analysis set (FAS) will include all enrolled subjects who receive at least 1 dose of study drug and will be used in both efficacy and safety analyses.

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13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by dose regimen and overall based on all enrolled subjects. 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 therapeutic class and preferred name.

13.1.3 Safety Analysis

The primary objective of the study is to determine the safety profile of long-term vedolizumab IV treatment in pediatric subjects with UC or CD. Safety analyses will be performed using the FAS. Safety data will be summarized by dose regimen and various subgroups including by indication (UC or CD). No statistical inference will be made for safety analyses.

Treatment-emergent AEs (TEAEs) are undesirable events not present prior to medical treatment or an already-present event that worsens either in intensity or frequency following the treatment, occurring from the first dose of study drug to the day of last dose of study drug + 126 days (accounting for 5 times the half-life of vedolizumab). The number and percentage of subjects with TEAEs (defined as any AE, regardless of relationship to study drug), CCI 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. TEAEs will also be summarized by severity and by relationship to study drug. Separate summaries will be generated for treatment-related AEs overall and by severity. Exposure-adjusted incidence rates will also be analyzed.

CCI

Physical examination findings CCI will be presented in data listings.

13.1.4 Efficacy Analysis

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13.1.5 CCI

[redacted]

13.1.6 Other Analyses

Secondary objectives of the study include determining the effect on patterns of growth and development, health-related quality of life measurements, and time to major IBD-related events.

Time to major IBD-related events (hospitalizations, surgeries, and procedures) will be analyzed and Kaplan-Meier estimates presented every 48 weeks.

Change from Baseline in IMPACT-III total and subscale scores, height, CCI [redacted], weight, and BMI will be summarized descriptively by dose regimen. Height velocity will be summarized by visit. The percentage of subjects achieving Tanner stage V at or before age 16 years (females) or 17 years (males) will be summarized by dose regimen.

CCI [redacted]

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13.2 Interim Analysis

Several interim analyses may be conducted to support future pediatric studies. These may occur 1) when all subjects in the ≥30 kg weight group have completed Week 32 or withdrawn from the study or 2) when all subjects in the <30 kg weight group have completed Week 32 or withdrawn from the study. The purpose of conducting interim analyses would be to gain intermediate information on CCI efficacy, and safety and results may be used to inform design and dose selection for other pediatric studies. There is no intention for early trial termination based on the results of the interim analysis (other than safety concerns).

13.3 Determination of Sample Size

Due to no hypothesis testing, there were no formal sample size calculations done for this study. It is estimated that up to 80 subjects (40 with UC and 40 with CD) who completed Study MLN0002-2003 will enter this study.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent/assent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent/assent 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.

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches, such as remote source data verification or telephone contact, may be used. Alternative monitoring approaches should be used only where allowed by the local health authority and permitted by the IRB/IEC, if required.

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.

Takeda will notify the concerned EU Member States of a serious breach of EU Clinical Trial Regulation (CTR) or the applicable protocol version through the EU portal not later than 7 days after becoming aware of the breach. In this instance a "serious breach" is one likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of trial data. All parties involved in the conduct of the clinical trial must immediately report any events they encounter that might meet the definition of a serious breach to the contact point designated in the applicable study document.

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 its 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 documents will embody the elements of informed consent/pediatric assent 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 authorized representative may provide such consent/assent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally authorized 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 authorized 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 authorized representative, at the time of consent/assent and prior to the subject entering into the study. The subject or the subject's legally authorized 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 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.

All revised informed consent/assent forms must be reviewed and signed by relevant subjects or the relevant subject's legally authorized representative in the same manner as the original informed consent/assent. The date the revised consent/assent was obtained should be recorded in

the subject's medical record, and the subject should receive a copy of the revised informed consent/assent form.

15.2.1 Informed Consent for Use of Remaining Samples

Consent will be obtained separately for the future use of samples. Those not consenting to the future use of samples, or withdrawing consent for this at any time, will be able to participate in all other portions of the trial unimpeded and without bias to their care.

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.

In the event that a serious data breach is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventative actions in response. These actions will be documented, and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study subjects, this would be done through the investigator.

Takeda applies certain measures to protect participants' personal data and prevent data breaches, detailed in a separate document (Compliance with National Requirements on Data Protection).

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study

information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

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

15.4.2 Clinical Trial Registration

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

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

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

15.4.3 Clinical Trial Results Disclosure

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

EU has a specific demographic breakdown that is required for all studies by age and enrollment by country. For this study, children (aged 2 to 11 years) and adolescents (aged 12 to 17 years) will be summarized.

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.

16.0 REFERENCES

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Appendix A Schedule of Study Procedures

Study Procedures	Pre-enrollment (a)	Day 1 (+1 wk) (b)	Year 1 through 5 (c) Weeks (±3 days) (d)													Unscheduled Visit (e)	Final Visit/ ET Visit (f)	Follow-Up Safety Visit (f)
			8	16	24	32	40	48	56	64	72	80	88	96	104			
			112	120	128	136	144	152	160	168	176	184	192	200	208			
			216	224	232	240	248	256	264	272	280	288	296	304	312			
			320	328	336	344	352	360	368	376	384	392	400	408	416			
			424	432	440	448	456	464	472	480	488	496	504	512	520			
			528	536	544	552	560	568	576	584	592	600 (c)					±3 days	±1 wk
Informed consent/pediatric assent (g)		X																
Inclusion/exclusion		X																
PML wallet card		X																
Allergy reaction card		X																
Demographics	(P)																	
Medical history (h)	(P)	X																
Medication history	(P)	X																
UC/CD prior biologics history	(P)																	
IRT/drug dispensing		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Dosing (i)		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Physical examination (j,k)	(P)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight (k,l)	(P)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height (k)	(P)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (k)	(P)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]																		
Concomitant medications (n)	(P)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant procedures (n)	(P)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment (h)	(P)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE assessment (h)	(P)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

Study Procedures	Pre-enrollment (a)	Day 1 (+1 wk) (b)	Year 1 through 5 (c) Weeks (±3 days) (d)													Unscheduled Visit (e)	Final Visit/ ET Visit (f)	Follow-Up Safety Visit (f)
			8	16	24	32	40	48	56	64	72	80	88	96	104			
			112	120	128	136	144	152	160	168	176	184	192	200	208			
			216	224	232	240	248	256	264	272	280	288	296	304	312		±3 days	±1 wk
			320	328	336	344	352	360	368	376	384	392	400	408	416			
			424	432	440	448	456	464	472	480	488	496	504	512	520			
			528	536	544	552	560	568	576	584	592	600 (c)						
Tanner stage evaluation		X	To be completed q 16 weeks: Wk 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 384, 400, 416, 432, 448, 464, 480, 496, 512, 528, 544, 560, 576, and 592														X	
Urine pregnancy test (o)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry	(P)		To be completed q 16 weeks: Wk 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 384, 400, 416, 432, 448, 464, 480, 496, 512, 528, 544, 560, 576, and 592													X	X	X
Hematology (p)	(P)		To be completed q 16 weeks: Wk 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 384, 400, 416, 432, 448, 464, 480, 496, 512, 528, 544, 560, 576, and 592													X	X	X
CCI [redacted]																		
Fecal calprotectin (s)		X	To be completed q 48 weeks: Wks 48, 96, 144, 192, 240, 288, 336, 384, 432, 480, 528, and 576													X	X	
Stool sample for culture (t)																X		
CCI [redacted]																		
Subject diary dispensed (u)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PUCAI (v)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PCDAI (v)		X	To be completed q 16 weeks: Wk 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 384, 400, 416, 432, 448, 464, 480, 496, 512, 528, 544, 560, 576, and 592													X	X	

Study Procedures	Pre-enrollment (a)	Day 1 (+1 wk) (b)	Year 1 through 5 (c) Weeks (±3 days) (d) 8	16	24	32	40	48	56	64	72	80	88	96	104	Unscheduled Visit (e)	Final Visit/ ET Visit (f)	Follow-Up Safety Visit (f)
			112	120	128	136	144	152	160	168	176	184	192	200	208			
			216	224	232	240	248	256	264	272	280	288	296	304	312		±3 days	±1 wk
			320	328	336	344	352	360	368	376	384	392	400	408	416			
			424	432	440	448	456	464	472	480	488	496	504	512	520			
			528	536	544	552	560	568	576	584	592	600 (c)						
Partial Mayo (UC subjects)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CCI [redacted]																		
Complete Mayo (x) (UC subjects)/ SES-CD (CD subjects)			To be completed at Week 32 CCI [redacted]														X	
CDAI (y)			To be completed at Week 32 CCI [redacted]															
IMPACT-III (z)		X	To be completed q 24 weeks: Wks 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504, 528, 552, 576, and 600															

d=day, wk=week.

(a) (P)=previous (data obtained from Study MLN0002-2003).

(b) Day 1 will be after completion of MLN0002-2003 Week 22 assessments or up to 1 week after. If the MLN002-2003 Week 22 and Vedolizumab-2005 Day 1 visits coincide, the Day 1 procedures do not need to be repeated.

(c) Duration of vedolizumab IV treatment will vary by subject on the basis of continued benefit but will be until vedolizumab IV is available for pediatric indication(s) in the subject's country or until other drug access programs become available (whichever comes first), the subject turns 18 years of age and can be transitioned to commercial drug, the subject withdraws from the study, or the sponsor decides to close the study.

(d) If a clinic visit must be conducted via alternative methods because of a pandemic (eg, coronavirus pandemic 2019), safety laboratory assessments may be done using local laboratories if it is feasible for the subject to visit a local laboratory sooner than the study site for sample collection. See Section 9.3.8 for guidance on alternative methods for conducting study procedures due to a pandemic.

(e) 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.

(f) Subjects who discontinued from the study for any reason will complete the ET Visit. All subjects will complete a Final Safety Visit 18 weeks (±1 week) after their last dose of study drug, as well as the long-term follow-up safety survey by telephone 6 months after their last dose of study drug.

(g) Informed consent/assent may be obtained starting at Week 14 of MLN0002-2003. Depending on relevant regulatory guidelines, the subject may need to re-provide informed consent as an adult during this study.

(h) Collection of AEs and SAEs will commence from the time the subject is administered study drug in this study and will continue through Final Safety Visit. AE/SAE assessment must be conducted on Day 1 if the previous data (obtained from Study MLN0002-2003) was collected before Day 1. Events that were reported as AEs or SAEs in Study MLN0002-2003 need to be recorded on the Medical History for Study Vedolizumab-2005. Events that were reported as AEs or SAEs in Study MLN0002-2003 that were ongoing at the end of that study need to be re-recorded as AEs for Study Vedolizumab-2005 if they change in severity.

(i) Subjects will initially receive vedolizumab IV at the same dose administered at Week 14 in Study MLN0002-2003. At the discretion of the investigator, subjects receiving the low dose (150 mg for subjects ≥30 kg; 100 mg for subjects <30 kg) vedolizumab IV who demonstrate disease worsening by PUCAI/PCDAI at 2 consecutive visits (scheduled or unscheduled) may dose escalate to high dose (300 for subjects ≥30 kg; 200 mg for subjects <30 kg) vedolizumab IV Q8W based on weight at the time of nonresponse.

(j) Physical examination: clinically significant findings will be recorded as medical history if start is prior to signing the informed consent/pediatric assent, or as AEs if start is after the first dose of study drug.

(k) To be performed prior to dosing.

(l) After completion of Study MLN0002-2003, subjects who have dose increased based on nonresponse should be dosed based on weight at the time of nonresponse (Table 8.a).

CCI [redacted]

(n) Monitoring of concomitant medications and concomitant procedures will begin at signing of the informed consent/pediatric assent.

(o) A urine pregnancy test will be completed for all females of child-bearing potential prior to each dose of study drug and at the ET/Final Safety Visit.

(p) The ESR may be performed at a local laboratory.

CCI [redacted]

(s) A stool sample will be collected for the analysis of fecal calprotectin (a biomarker of intestinal inflammatory activity) every 48 weeks, when a subject becomes symptomatic (eg, worsening of disease activity), and at ET/Final Safety Visit. The stool sample for the analysis of fecal calprotectin must be collected before any bowel preparation is given for endoscopy and before dosing.

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

(u) For scheduled visits, the daily diaries for the next scheduled visit (7 for UC and 10 for CD) can be dispensed when the patient leaves the office from the last visit. The subject will then start filling them out 7 days prior to the next scheduled visit (for UC) or 10 days prior to the next scheduled visit (for CD) and then return the completed diaries when they come for the visit. For unscheduled visits due to flares, the subject should start filling out daily diary sheets when the flare begins (if possible) and then come in for the unscheduled visit for evaluation. A flare is confirmed by observing the subject during a one-week interval (to confirm that it is ongoing) and during that week, the diaries can continue to be filled out to make sure the subject has 7 days of symptom diaries if they have UC and 10 days of symptom diaries if they have CD. Also: 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.

(v) The components of the PUCAI/PCDAI scores can be completed within 7 days prior to receiving study drug.

CCI

(x) The complete Mayo assessment includes the Mayo endoscopic subscore.

(y) The CDAI will be completed when an endoscopy is performed.

(z) The IMPACT-III questionnaire (where translations are available) will be administered to subjects, aged 9 to 17 years at the time of first dose of study drug in Study Vedolizumab-2005, every 24 weeks from Week 24.

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 by 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 authorized 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/Parental Informed Consent/Pediatric Assent

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

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally authorized 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 authorized 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 authorized representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:

    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;

    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;

    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and efficacy of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;

    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

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

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use 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.
26. 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 treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

Appendix E Sponsor Responsibilities

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current ICH GCP Guidelines, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, participants' source documents, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required before release of study intervention for shipment to the site.

Appendix F 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 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 subject'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.

PCDAI Scoring				
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 Mayo Scoring System for the Assessment of UC 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 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 Tanner Scale

Puberty and the Tanner Stages - developed by Professor James M Tanner

Introduction

Adolescents experience several types of maturation, including cognitive (the development of formal operational thought), psychosocial (the stages of adolescence), and biologic. The complex series of biologic transitions are known as puberty, and these changes may impact psychosocial factors.

The most visible changes during puberty are growth in stature and development of secondary sexual characteristics. Equally profound are changes in body composition; the achievement of fertility; and changes in most body systems, such as the neuroendocrine axis, bone size, and mineralization; and the cardiovascular system. As an example, normal cardiovascular changes, including greater aerobic power reserve, electrocardiographic changes, and blood pressure changes, occur during puberty.

The normal sequence of pubertal events and perils of puberty are reviewed here. This is within the normal ranges and does not take into account Precocious Puberty or Delayed Puberty.

Tanner Stages

Conceptually, pubertal maturation can be described in terms of sequence, timing, and tempo (Puberty consists of a series of predictable events, and the sequence of changes in secondary sexual characteristics has been categorized by several groups. The staging system utilized most frequently is that published by Marshall and Tanner and the sequence of changes, commonly referred to as “Tanner stages”, is described below.

Boys - development of external genitalia

Stage 1:	Prepubertal
Stage 2:	Enlargement of scrotum and testes; scrotum skin reddens and changes in texture
Stage 3:	Enlargement of penis (length at first); further growth of testes
Stage 4:	Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotum skin darker
Stage 5:	Adult genitalia

Girls - breast development

Stage 1:	Prepubertal
Stage 2:	Breast bud stage with elevation of breast and papilla; enlargement of areola
Stage 3:	Further enlargement of breast and areola; no separation of their contour
Stage 4:	Areola and papilla form a secondary mound above level of breast
Stage 5:	Mature stage: projection of papilla only, related to recession of areola

Boys and girls - pubic hair

Stage 1:	Prepubertal (can see vellus hair similar to abdominal wall)
Stage 2:	Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia
Stage 3:	Darker, coarser and more curled hair, spreading sparsely over junction of pubes
Stage 4:	Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs
Stage 5:	Adult in type and quantity, with horizontal distribution ("feminine")

Boys Growth

- Stage 1: 5-6 cm/year.
- Stage 2: 5-6 cm/year.
- Stage 3: 7-8 cm/year.
- Stage 4: 10 cm/year.
- Stage 5: No further height increase after 17 years.

Girls Growth

- Stage 1: 5-6 cm/year.
- Stage 2: 7-8 cm/year.
- Stage 3: 8 cm/year.
- Stage 4: 7 cm/year.
- Stage 5: No further height after 16 years.

Source: Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969 Jun; 44(235): 291–303. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in boys. Arch Dis Child. 1970 Feb; 45(239): 13–23.

Appendix K 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/ideal weight for height)]×100		×1	
Final score			Add totals:	

Source: Adapted from: Best WR, Beckel 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) To calculate body weight:

1. Identify the weight in kilogram (kg) for this visit.
2. Find the child's measured height to determine the percentile for that height by gender and age, using Centers for Disease Control and Prevention Stature-for-Age growth chart (cdc.gov/growthcharts/html_charts/statage.htm).
3. The child's Ideal Weight for Height is the weight on the same percentile for the child's gender and age, using Centers for Disease Control and Prevention Weight-for-Age growth chart. For example, for a boy's height at the 25th percentile for his age, his ideal weight will be considered to also be the 25th percentile weight for his age (cdc.gov/growthcharts/html_charts/wtage.htm)
4. Calculate the total score using the formula above, rounding to the nearest integer. If the body weight total score is <-10, the body weight total score is set to -10.

Appendix L Protocol History Appendix

Date	Amendment Number	Region
27 September 2024	8	Global
08 March 2023	7	Global
01 December 2021	6	Global
24 August 2018	05	Global
13 February 2018	04	Global
13 October 2017	03	Local/United Kingdom
25 May 2017	02	Global
07 April 2017	01	Global
17 October 2016	Initial version	Global

Protocol Amendment 7 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 7. The primary reasons for this amendment are to:

- Describe the management of study procedures to maintain subject safety, confidentiality, and study integrity in the context of healthcare delivery challenges due to a pandemic (eg, coronavirus disease 2019 [COVID-19]).
- Remove the data and safety monitoring board.
- Remove the Risk Assessment and Minimization Program for Progressive Multifocal Leukoencephalopathy.
- Describe posttrial access to vedolizumab.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 7			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Figure 6.a Schematic of Vedolizumab-2005 Study Design Section 6.2.1 Justification for Study Design and Endpoints Section 8.1.3 Dose and Regimen Section 9.3.2 Final Visit or ET Section 9.3.5 Poststudy Care Appendix A Schedule of Study Procedures	Updated the duration of vedolizumab intravenous (IV) treatment to allow treatment to continue until vedolizumab IV is commercially available for pediatric indication(s) in the subject's country or until other drug access programs become available (whichever comes first), the subject turns 18 years of age and can be transitioned to commercial drug, the subject withdraws from the study, or the sponsor decides to close the study.	Change made to ensure uninterrupted study medication availability for subjects who continue to receive clinical benefit from vedolizumab IV treatment.
2.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria Section 7.3.1.1 Oral Corticosteroid Dosing	Clarified acceptable use of corticosteroids.	Change made to ensure that corticosteroids are not introduced during Vedolizumab-2005.
3.	Section 6.2.1 Justification for Study Design and Endpoints Section 6.3.1 Criteria for Premature Termination or Suspension of the Study Section 11.1 Independent Data Safety Monitoring Board (deleted)	Removed the data and safety monitoring board (DSMB).	This committee was no longer required for this open-label study once the last subject reached the Week 40 visit of Vedolizumab-2005 (the DSMB members endorsed decommissioning of the DSMB after subject dosing was unblinded).
4.	Section 4.1.3.2 Clinical Section 4.3 Benefit/Risk Assessment	Updated content to include information on conduct of completed pediatric study MLN0002-2003 and availability of data from completed pediatric study and the vedolizumab development program. Included reference to current edition of Investigator's Brochure as the most up-to-date source for clinical experience data.	Revised to provide the most current information for vedolizumab.

Protocol Amendment 7			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
5.	Section 6.1 Study Design Section 9.3.4 Long-term Follow-up Safety Survey Section 9.3.5 Poststudy Care	Added posttrial access information for vedolizumab and clarified safety follow-up procedures.	Revised to ensure that subjects completing the study will have an option to continue vedolizumab treatment.
6.	Section 6.2.1 Justification for Study Design and Endpoints Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject Section 9.1.19 PML Checklist (deleted) Section 9.3.6 Unscheduled Visits Due to Disease Exacerbation Section 11.2.1 RAMP Program (deleted) Section 13.1.3 Safety Analysis Appendix A Schedule of Study Procedures	Removed the Risk Assessment and Minimization Program for Progressive Multifocal Leukoencephalopathy (RAMP).	Change made because the RAMP is no longer required, per Food and Drug Administration (FDA) communication.
7.	Section 9.1.6.1 Completion and Review of Entries to Diaries	Added reference to Pediatric Crohn's Disease Activity Index (PCDAI) completion with links to the correct appendices.	Corrected an omission.
8.	Section 9.3.2 Final Visit or ET Appendix A Schedule of Study Procedures	Clarified that treatment will vary by subject on the basis of continued benefit but will be until vedolizumab IV is commercially available for pediatric indication in the subject's country or until other drug access programs become available (whichever comes first), the subject turns 18 years of age and can be transitioned to commercial drug, the subject withdraws from the study, or the sponsor decides to close the study. Also added a column for the safety follow-up visit.	Revised to clarify that dosing continues throughout a subject's participation, as defined in the description. The column for the safety follow-up visit detailing the assessments to be performed had been unintentionally omitted and has now been added.

Protocol Amendment 7			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
9.	Section 9.3.8 Alternative Approaches to Study Procedures and Data Collection Due to a Pandemic Section 14.1 Study-Site Monitoring Visits Appendix A Schedule of Study Procedures	Added guidance on alternative approaches to executing study procedures and collecting study data due to a pandemic (eg, the coronavirus disease 2019 [COVID-19] pandemic or other future similar unexpected public health concern requiring physical distancing), including use of local laboratories, remote visits, and remote monitoring visits.	Addition made to provide flexibility in administration of study procedures during a pandemic (eg, the COVID-19 pandemic or other future similar unexpected public health concern requiring physical distancing), while ensuring the safety of study participants, maintaining compliance with Good Clinical Practice, and minimizing risks to study integrity.
10.	Section 10.2.1.4 AESI Reporting	CCI [redacted]	CCI [redacted]
11.	Section 15.4.3 Clinical Trial Results Disclosure	Added information about results required for disclosure per the European Union.	Addition made to ensure that the required data summaries-by-age are clear.
12.	Appendix A Schedule of Study Procedures	Clarified that PCDAI scoring is completed every 16 weeks, rather than every 8 weeks, in alignment with collection of laboratory results.	Laboratory results collected (hematocrit, albumin and erythrocyte sedimentation rate) are key elements of the PCDAI (Crohn's disease activity) scoring. Laboratory results are collected every 16 weeks; therefore the PCDAI scoring should follow this same schedule. This aligns with protocol Section 9.1.6.1 Completion and Review of Entries to Diaries.

Protocol Amendment 6 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 6. The primary reason for this amendment is to:

- Align the legal entity (sponsor) name across Takeda studies.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 6			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Cover page	Removed Takeda Development Centre (TDC) Europe as a sponsor and updated the address for TDC Americas.	Revised to align the sponsor name across Takeda studies and correct the address for TDC Americas.
2	1.1 Contacts	Revised the identified contacts.	Changes made to reflect currently available representatives to contact.
3	Section 1.2 Approval	Revised the identified approvers.	Changes made based on current functional area representatives approving this document.

Rationale for Amendment 05

This document describes the changes in reference to the Protocol Incorporating Amendment No. 05. The primary purpose of this amendment is to add patient diaries for symptom assessment and clarify the required evaluation tools to be used when an endoscopy is performed.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

Changes in Amendment 05

1. Revised text to align with Core Data Sheet.
2. Specified that the endoscopic subscore is included in the complete Mayo assessment for patients with ulcerative colitis, and clarified that the complete Mayo score for patients with ulcerative colitis, or the simple endoscopic score for Crohn's disease, and Crohn's Disease Activity Index for patients with Crohn's disease, are generated at Week 32 CCI [redacted]
3. Added completion and review of patient diaries.
4. Added Crohn's Disease Activity Index questionnaire as a new appendix.

Rationale for Amendment 04

This document describes the changes in reference to the Protocol Incorporating Amendment No. 04. The primary purposes of this amendment are to incorporate initial blinding of dosing; to add an additional, required endoscopy; and to clarify Inclusion Criteria and Exclusion Criteria, the definition of disease worsening and concomitant medication usage.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

Changes in Amendment 04

1. Clarified the definition of disease worsening after dose escalation.
2. Added previously omitted additional endpoints.
3. Deleted Harvey Bradshaw Index.
4. Incorporated initial blinding to dose.
5. Clarified eligibility and enrollment procedures.
6. Clarified Inclusion Criterion 4.
7. Deleted Inclusion Criterion 5.
8. Amended Exclusion Criterion 10.
9. Clarified permitted medications during the study.
10. Amended the concomitant oral corticosteroid dosing information.
11. Defined chronic nonsteroidal anti-inflammatory drug use.
12. Specified that the erythrocyte sedimentation rate may be performed at a local laboratory.
13. Removed urinalysis.
14. Deleted Section 9.1.15.4.

CCI [redacted]

[redacted]

CCI [redacted]

18. Clarified the End of Study definition.
19. Amended interim analysis language.
20. Updated the protocol deviation information.
21. Removed electrocardiogram assessments.

Rationale for Amendment 03

This document describes the changes in reference to the Protocol Incorporating Amendment No. 03. The primary purposes of this amendment are to clarify Inclusion Criterion 4 and the definition of disease worsening.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

Changes in Amendment 03

1. Clarified Inclusion Criterion 4.
2. Clarified the definition of disease worsening.
3. Clarified the End of Study definition.

Rationale for Amendment 02

This document describes the changes in reference to the Protocol Incorporating Amendment No. 02. The primary purpose of this amendment is to update the EudraCT number.

Changes in Amendment 02

1. Update to the EudraCT number.

Rationale for Amendment 01

This document describes the changes in reference to the Protocol Incorporating Amendment No. 01. The primary purpose of this amendment is to update the protocol to allow enrollment of pediatric subjects aged 2 to 17 years, inclusive, who weigh <30 kg. The vedolizumab IV dose and dosing regimen for subjects in this weight category was added. Other minor changes in procedures are proposed. Minor grammatical and editorial changes are included for clarification purposes only.

Changes in Amendment 01

1. Update to allow enrollment of pediatric subjects who weigh <30 kg.
2. Corrected typographical errors, punctuation, grammar, and formatting.

Signature Page for Vedolizumab-2005-Protocol-Amendment #8-27-Sep 2024
Title: Vedolizumab-2005-Protocol-Amendment #8-27-Sep 2024

Approval	PPD Clinical 27-Sep-2024 14:40:32 GMT+0000
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