Clinical Study Protocol

NCT Number: NCT04779307

Title: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of Vedolizumab Intravenous as Maintenance Therapy in Pediatric Subjects With Moderately to Severely Active Ulcerative Colitis Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy

Study Number: MLN0002-3024

Document Version and Date: Amendment 7, 27 Feb 2025

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.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of Vedolizumab Intravenous as Maintenance Therapy in Pediatric Subjects with Moderately to Severely Active Ulcerative Colitis Who Achieved Clinical Response Following Open-label Vedolizumab Intravenous Therapy

Sponsor:	Takeda Development Center Americas, Inc. 500 Kendall Street, Cambridge, MA 02142		
Study Number:	MLN0002-3024		
IND Number:	009125	**EU CT Number:**	2023-509018-12
Compound:	Vedolizumab IV		
Date:	27 February 2025	**Version/Amendment Number:**	7

Amendment History:

Date	Amendment Number	Region
27 February 2025	7	Global
19 September 2024	6	Global
03 July 2024	5	Global
08 September 2023	4	Global
28 November 2022	3	Global
13 October 2021	2	Global
16 February 2021	1	Global
14 October 2020	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 (TDC)-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 medical 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 study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- Regulation (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 are provided on the last page of this document.

PPD , MD PPD , Clinical Science	Date	PPD , MPH PPD , GI2 Statistics Statistical and Quantitative Sciences, Data Sciences Institute	Date
PPD , Ph.D PPD , Quantitative Clinical Pharmacology	Date	PPD , MD PPD	Date
PPD , MD PPD , GI2 Pharmacovigilance	Date		

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- 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 study site agreement.
- Responsibilities of the Investigator (Appendix C).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix F 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 7 Summary of Changes

Protocol Amendment 7 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment No. 7. The primary reasons for this amendment are to:

- Amended process to allow for an additional interim analysis (Week 54 IA) once all subjects have completed Week 54 or prematurely discontinued.
- Clarified details for unblinding of Sponsor study team compared to subjects, legal representatives, and physicians. Added that the Sponsor study team will be unblinded at DBL for Week 54 IA, prior to completion of subject follow-up visits.

In this amendment, administrative changes not affecting the conduct of the study and correction to text 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 1.2 Approval	The name of the responsible Takeda medical director for pharmacovigilance and director for statistics signatories were updated.	Signatories updated to only include blinded team members as per the data access management plan.
2.	Section 9.1.15 Fecal Calprotectin Sample Collection	Corrected text for stool sample collection from 'Week 14' to 'Week 54'	Corrected typographical error.
3.	Section 13.1.6 Safety Analysis	Clarified all data at 'final' database lock with be summarized and additional data collected after final database lock will be provided as a CSR addendum.	Clarification.
4.	Section 13.2 IA and Criteria for ET	Added text that a further IA (Week 54 IA) may be performed once 'all subjects have completed the study through Week 54 or prematurely discontinued', and clarified timing of unblinding of the study team and study subjects and physicians in context of this IA.	To allow an additional IA to be performed once all subjects have completed Week 54.

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc.	**Compound:** Vedolizumab IV	
Title of Protocol: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of Vedolizumab Intravenous as Maintenance Therapy in Pediatric Subjects with Moderately to Severely Active Ulcerative Colitis Who Achieved Clinical Response Following Open-label Vedolizumab Intravenous Therapy	**IND No.:** 009125	**EU CT No.:** 2023-509018-12
Study Number: MLN0002-3024	**Phase:** 3	

Study Design: This is a phase 3 study of vedolizumab administered during a 14-week, open-label induction period followed by a 40-week, 2-dose arm, randomized, double-blind maintenance period designed to evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of high and low doses in 3 different weight groups of vedolizumab intravenous (IV) for maintenance of remission in children aged 2 to 17 years, inclusive, who weigh ≥10 kg with moderately to severely active ulcerative colitis (UC). The data from this study will be used for partial extrapolation of efficacy from adults to pediatric subjects based on the efficacy, safety, and PK data from completed studies in adult subjects.

Screening: Subjects must have been diagnosed with moderately to severely active UC for at least 1 month before screening and failed response to, lost response to, or been intolerant to at least 1 of the current standard of care (SOC) induction and maintenance therapies for UC, including immunomodulators (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate [MTX]), and tumor necrosis factor-alpha (TNF-α) antagonists (eg, infliximab, adalimumab). Lack of response to corticosteroids at the time of the initial diagnosis of UC or inability to wean off corticosteroids without a recurrence of symptoms will also qualify a subject for the study. Subjects or their legally authorized representative (or adult caregivers) will be provided with an electronic symptom diary and trained on its use during the initial screening visit and will complete the symptom diary daily throughout participation in the study. Subjects will be evaluated during a 35-day screening period by using symptom diaries, colonoscopy, and determination of fecal calprotectin and C-reactive protein (CRP). Those with moderately to severely active UC, defined by a modified Mayo score (see Appendix I and Appendix L) of 5 to 9 (sum of the stool frequency, rectal bleeding, and endoscopic subscores with an endoscopic subscore of ≥2), can enter the open-label induction period. The Pediatric Ulcerative Colitis Activity Index (PUCAI) will also be assessed (see Appendix J and Appendix L). All colonoscopies (at screening and all subsequent flexible sigmoidoscopies at Weeks 14 and 54 or the early termination [ET] visit) will be centrally read for Mayo endoscopic subscore. Historical colonoscopy (with recorded video) done up to 30 days prior to signing of assent/informed consent, can be submitted to central readers for assessment after assent/informed consent is obtained. If found to be adequate by central readers, this video colonoscopy will be used for the assessment of Mayo endoscopic subscore, which can be used as the baseline assessment.

Induction Period: On Day 1, the modified Mayo score should be verified and documented before infusion. During the induction period, subjects ≥30 kg will receive open-label vedolizumab, 300 mg IV at Day 1, Week 2, and Week 6; subjects who weigh >15 to <30 kg will receive an open-label dose of vedolizumab 200 mg IV at Day 1, Week 2, and Week 6; and subjects who weigh 10 to 15 kg will receive an open-label dose of vedolizumab 150 mg IV at Day 1, Week 2, and Week 6. Given the similarity of disease between adults and children with inflammatory bowel disease (IBD), a similar response is expected with a similar target vedolizumab exposure. Hence, selection of dose for the induction and maintenance phase was based on matching the adult exposure range. These doses were determined using an established population PK model, developed using data from adult phase 3 studies and the pediatric phase 2 study (MLN0002-2003) for ≥30 kg and <30 kg cohort, to match the vedolizumab exposure seen in the adult populations during the induction phase. Approximately 120 subjects will be enrolled in the induction period with around three-fourths of subjects weighing ≥30 kg and around one-fourth of subjects weighing 10 to <30 kg at the time of enrollment into the study.

Weight Group [a]	Induction Dose
Subjects ≥30 kg	300 mg IV at Day 1, Week 2, and Week 6
Subjects >15 to <30 kg	200 mg IV at Day 1, Week 2, and Week 6
Subjects 10 to 15 kg	150 mg IV at Day 1, Week 2, and Week 6

IV: intravenous.
[a] No change in induction dose for weight change over time

At Week 14, all subjects will be evaluated for clinical response, based on modified Mayo score (defined as a reduction of ≥2 points and ≥30% from the baseline modified Mayo score with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point). Those who do not achieve a clinical response during the open-label induction period will discontinue study treatment, complete the ET visit, and will proceed to the follow-up safety assessment 18 weeks after their last dose of study drug. Nonresponders will enter Study MLN0002-3029 for an observational long-term follow-up (LTFU) period of 2 years after last dose of study drug. During the LTFU period, data will be collected either by clinic visit or, if site attendance is not feasible, will be collected by phone call every 6 months.

Randomization Into the Maintenance Period: At Week 14, those who achieve **clinical response** (defined as a reduction of ≥2 points and ≥30% from the baseline modified Mayo score with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point) will be stratified by previous exposure/failure to TNF-α antagonists therapy or naive to TNF-α antagonists therapy, and by weight group (≥30 kg; >15 kg to <30 kg; 10 kg to 15 kg). Subjects will be randomized 1:1 to one of the 2 vedolizumab dose groups (high dose, low dose), within each of the 3 weight groups (≥30 kg; >15 kg to <30 kg; 10 kg to 15 kg), for the double-blind maintenance period.

Weight Group [a]	High Dose	Low Dose
Subjects ≥30 kg	300 mg IV Q8W	150 mg IV Q8W
Subjects >15 to <30 kg	200 mg IV Q8W	100 mg IV Q8W
Subjects 10 to 15 kg	150 mg IV Q8W	100 mg IV Q8W

IV: intravenous; Q8W: once every 8 weeks.
[a] During the maintenance period, adjustments to the dose will be as described for lack of maintenance of clinical response and worsening of disease only; no adjustments made strictly on the basis of weight change over time.

Maintenance Period: Subjects who qualify as responders at the end of the induction period (Week 14) will initiate blinded IV doses of vedolizumab once every 8 weeks (Q8W) as maintenance dose through Week 46. The maintenance doses for the 3 weight groups were chosen similar to the way induction doses were chosen. A population PK model was used to match the vedolizumab exposure seen in phase 3 studies for the adult population during the maintenance phase. The high and low doses were selected to maximize the dose difference between the 2 arms while maintaining the exposure within the adult population range. Based on the chosen induction dose, high and low maintenance doses of 300 mg and 150 mg were chosen for the ≥30 kg weight group, 200 mg and 100 mg were chosen for the >15 to <30 kg weight group, and 150 mg and 100 mg were chosen for the 10 to 15 kg weight group. A 150 mg high maintenance dose in the 10 to 15 kg weight group was predicted to result in an exposure closer to, but not exceeding, the upper limit of the adult exposure in the maintenance phase. Similarly, a 100 mg low maintenance dose was predicted to result in an exposure closer to, but not below, the lower limit of adult exposure in the maintenance phase. A 100 mg low maintenance dose was predicted to result in similar and consistent exposure among the entire <30 kg weight groups. A dose of 75 mg was considered for the low maintenance dose in the 10 to 15 kg weight cohort; however, this would have resulted in an exposure less than adult phase 3 exposure.

Lack of maintenance of clinical response and worsening of disease:

At each visit before the infusion, clinical response based on partial Mayo score will be assessed. Improvement or maintenance of clinical response will result in continuation of the blinded dosing of vedolizumab IV. Lack of maintenance of clinical response and **worsening of disease** are defined as the following at 2 consecutive visits (scheduled or unscheduled) at least 7 days apart:

- Increase in the Mayo subscore of stool frequency by 1 point to at least ≥2 points AND

- Increase in the Mayo subscore of rectal bleeding by at least 1 point with an absolute bleeding subscore of ≥2 points.

In addition to safety assessments, PUCAI score calculation, and evaluation of symptoms and laboratory parameters indicative of disease activity at the applicable visits, an endoscopy will be performed at Week 54 to evaluate endoscopic response and remission. Blood samples will be collected for vedolizumab PK and immunogenicity evaluation throughout the study. Subjects who continue to maintain a corticosteroid-free clinical response at Week 54 will be eligible to receive study drug in the MLN0002-3029 extension study.

For subjects who do not maintain corticosteroid-free clinical response at Week 54, or who discontinue study drug at any time during the induction or maintenance periods of this study, final on-study assessments will include an end-of-study or ET visit and a follow-up safety visit 18 weeks after the last dose of study drug. These subjects will enter Study MLN0002-3029 for an observational LTFU period of 2 years after the last dose of study drug. During the LTFU period, data will be collected either by clinic visit or, if site attendance is not feasible, will be collected by phone call every 6 months.

Dose Escalation and Steroid Rescue During the Maintenance Period:

Lack of maintenance of clinical response and worsening of disease will result in a blinded dose escalation based on the subject's weight at the time of the worsening of disease, as described in the table below.

Weight Group (at Time of Randomization Into the Maintenance Period)	**Blinded Dose (at Randomization)**	**Weight Group (at Time of Disease Worsening)**	**Dose Escalation?**	**Blinded Dose (After Disease Worsening)**
10 to 15 kg	100 mg IV Q8W	10 to 15 kg	Yes	150 mg IV Q8W
		>15 to <30 kg	Yes	200 mg IV Q8W
		≥30 kg	Yes	300 mg IV Q8W
	150 mg IV Q8W	10 to 15 kg	No	150 mg IV Q8W
		>15 to <30 kg	Yes	200 mg IV Q8W
		≥30 kg	Yes	300 mg IV Q8W
>15 to <30 kg	100 mg IV Q8W	10 to 15 kg	Yes	150 mg IV Q8W
		>15 to <30 kg	Yes	200 mg IV Q8W
		≥30 kg	Yes	300 mg IV Q8W
	200 mg IV Q8W	10 to 15 kg	No	200 mg IV Q8W
		>15 to <30 kg	No	200 mg IV Q8W
		≥30 kg	Yes	300 mg IV Q8W
≥30 kg	150 mg IV Q8W	10 to 15 kg	No	150 mg IV Q8W
		>15 to <30 kg	Yes	200 mg IV Q8W
		≥30 kg	Yes	300 mg IV Q8W
	300 mg IV Q8W	10 to 15 kg	No	300 mg IV Q8W
		>15 to <30 kg	No	300 mg IV Q8W
		≥30 kg	No	300 mg IV Q8W

IV: intravenous; Q8W: once every 8 weeks.

In addition to dose escalation, lack of maintenance of clinical response and worsening of disease during the maintenance period will result in subject eligibility to receive rescue therapy with corticosteroids at the investigator's discretion in an attempt to re-establish response/remission. Those subjects whose dose is escalated and/or who receive rescue corticosteroids will, for the analysis of blinded maintenance dose groups, be considered nonresponders to the initial blinded dose of vedolizumab; however, they can remain in the study, and safety, PK, and efficacy data will continue to be assessed in this cohort for the duration of the study. If the investigator elects to continue the subject in the study and initiates corticosteroid rescue at a scheduled or unscheduled visit, it must be based on evaluation of partial Mayo score with documentation of worsening. Prescribed doses of corticosteroids at the discretion of the investigator should not exceed 40 mg or 1 mg/kg (whichever is lower) of oral prednisone per day or its equivalent. All subjects, including those initiated on corticosteroid rescue therapy who achieve no clinical response (as previously defined) in 2 subsequent consecutive visits should be discontinued from the study. After initiation of corticosteroid rescue therapy, tapering of corticosteroids will start if/when the subject has achieved clinical response based on partial Mayo score measured at the next scheduled or unscheduled follow-up visit. Corticosteroids will be tapered on a controlled schedule defined in the protocol designed to wean off corticosteroids within 12 weeks of initiation of tapering. Worsening of disease upon tapering of corticosteroids will result in discontinuation from the study, and the subject will proceed to the ET visit followed by the follow-up safety visit 18 weeks after their last dose of study drug and will enter study MLN0002-3029 for an observational LTFU period of 2 years after the last dose of study drug. During the LTFU period, data will be collected either by clinic visit or, if site attendance is not feasible, will be collected by phone call every 6 months.

Primary Objective:

To evaluate the efficacy of 2 different dose regimens of vedolizumab IV in pediatric subjects with moderately to severely active UC during maintenance therapy, based on clinical remission at Week 54.

Secondary Objectives:

The secondary objectives of this study are to evaluate:

- The efficacy of high and low doses of vedolizumab IV in pediatric subjects with moderately to severely active UC, based on clinical remission at Week 14.
- The efficacy of high and low doses of vedolizumab IV as measured by sustained clinical remission at Weeks 14 and 54.
- The efficacy of high and low doses of vedolizumab IV as measured by sustained clinical response at Weeks 14 and 54.
- The efficacy of high and low doses of vedolizumab IV as measured by sustained endoscopic remission at Weeks 14 and 54.
- The efficacy of high and low doses of vedolizumab IV as measured by endoscopic response at Weeks 14 and 54.
- The effect of high and low doses of vedolizumab IV on achieving corticosteroid-free remission at Week 54.
- The effect of high and low doses of vedolizumab IV on clinical response over time up to Week 54.
- The efficacy of high and low doses of vedolizumab IV as measured by clinical remission over time up to Week 54.
- Vedolizumab PK in pediatric subjects with moderately to severely active UC after IV administration.
- Safety in pediatric subjects on maintenance therapy up to Week 54.
- The immunogenicity of vedolizumab in pediatric subjects with moderately to severely active UC treated with vedolizumab IV.
- The effect of vedolizumab on patterns of growth and pubertal development in pediatric subjects with moderately to severely active UC during their participation in the study.

Exploratory Objectives:

The exploratory objectives of this study are to:

- Explore the relationship between vedolizumab exposure and the clinical and endoscopic response in pediatric subjects treated with vedolizumab IV during both induction and maintenance therapy.
- Assess markers of intestinal inflammation (CRP, serum albumin, fecal calprotectin) and analyze their correlation with trough PK levels of vedolizumab.
- Evaluate the quality of life in subjects aged 9 to 17 years who were treated with vedolizumab IV using the IMPACT-III questionnaire.
- Evaluate the efficacy of high and low doses of vedolizumab IV as measured by clinical remission based on PUCAI.
- Evaluate the efficacy of high and low doses of vedolizumab IV as measured by clinical response based on PUCAI.

Subject Population: Subjects aged 2 to 17 years, inclusive, with moderately to severely active UC, unresponsive or intolerant to their current SOC therapies for UC including: corticosteroids, immunomodulators (eg, AZA, 6-MP, MTX), and TNF-α antagonists (eg, infliximab, adalimumab).

Number of Subjects: approximately 120

Around three-fourths of subjects ≥30 kg for the induction period: responders at Week 14 randomized 1:1 to one of 2 blinded maintenance doses of vedolizumab.

Around one-fourth of subjects 10 to <30 kg for the induction period: responders at Week 14 randomized 1:1 to either a high or low blinded maintenance dose of vedolizumab.

Number of Sites:

Approximately 100 sites globally.

Dose Level(s):

Induction dose:

Vedolizumab: 300 mg (subjects ≥30 kg at the time of enrollment into the study).

Vedolizumab: 200 mg (subjects >15 to <30 kg at the time of enrollment into the study).

Vedolizumab: 150 mg (subjects 10 to 15 kg at the time of enrollment into the study).

Maintenance dose:

Vedolizumab: 300 mg or 150 mg (subjects ≥30 kg at the time of enrollment to the blinded maintenance dose).

Vedolizumab: 200 mg or 100 mg (subjects >15 to <30 kg at the time of enrollment to the blinded maintenance dose).

Vedolizumab: 150 mg or 100 mg (subjects 10 to 15 kg at the time of enrollment to the blinded maintenance dose).

Route of Administration:

IV

Duration of Treatment:

Open-label induction dose at Day 1, Week 2, and Week 6.

Double-blinded maintenance dose Q8W starting at Week 14 through Week 46.

Period of Evaluation:

The maximum period of evaluation from start of the screening period to 18-week follow-up safety visit is approximately 69 weeks. This includes:

- A screening period of up to 35 days.
- A 14-week induction period.

	• A 40-week maintenance period (with last dose at study Week 46). • An 18-week follow-up safety visit for those subjects who do not continue treatment with vedolizumab in extension study MLN0002-3029.

Potential Risks and Benefits

The proposed study will evaluate efficacy and safety of vedolizumab IV as maintenance therapy in pediatric subjects with moderately to severely active UC who achieve clinical response following open-label 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 existing therapy (including conventional therapy or TNF-α antagonists), or in whom side effects of these agents are intolerable or life threatening.

Vedolizumab IV has demonstrated statistically significant and clinically relevant evidence of effectiveness in multiple completed clinical studies in adult subjects with moderately to severely active UC. Similar clinical responses were observed in pediatric subjects with UC in study MLN0002-2003, as those seen in adults in previous phase 3 studies of vedolizumab IV induction therapy.

In clinical studies, vedolizumab IV has shown an acceptable and consistent safety profile in adults (≥18 years of age) with body weights ranging from 28.7 kg to 170 kg. In the pivotal phase 3 studies in adult UC subjects (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) have been related to exacerbations or complications of the underlying UC.

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 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, based on available clinical and postmarketing data, the benefit-risk profile in pediatric subjects with UC is expected to be positive. Further information on vedolizumab is provided in the current edition of the investigator's brochure**.**

Main Criteria for Inclusion:

1. The subject is aged 2 to 17 years, inclusive, at the time of screening and enrollment into the maintenance phase of the study.
2. The subject weighs ≥10 kg at the time of screening and enrollment into the study.
3. Subjects with UC diagnosed at least 1 month before screening. Subjects with moderately to severely active UC based on a modified Mayo score of 5 to 9 (sum of Mayo endoscopic subscore, stool frequency subscore, and rectal bleeding subscore) with a Mayo endoscopic subscore of ≥2 (with the presence of mucosal friability excluding an endoscopic subscore of 1 and mandating a score of at least 2) at screening endoscopy.
4. Subjects who have failed, lost response to, or been intolerant to treatment with at least 1 of the following agents: corticosteroids, immunomodulators (eg, AZA, 6-MP, MTX), and/or TNF-α antagonist therapy (eg, infliximab, adalimumab). This includes subjects who are dependent on corticosteroids to control symptoms and who are experiencing worsening of disease when attempting to wean off corticosteroids.
5. Subjects with evidence of UC extending proximal to the rectum (ie, not limited to proctitis), at a minimum.
6. Subjects with extensive colitis or pancolitis of >8 years' duration or left-sided colitis of >12 years' duration must have documented evidence of a negative surveillance colonoscopy within 12 months before screening.
7. Subjects with vaccinations that are up-to-date based on the countrywide, accepted schedule of childhood vaccines.

Main Criteria for Exclusion:

1. Subjects who have had previous exposure to approved or investigational anti-integrins including, but not limited to natalizumab, efalizumab, etrolizumab, or AMG 181, or mucosal addressin cell adhesion molecule-1 antagonists or rituximab.
2. Subjects who have had prior exposure to vedolizumab.
3. Subjects with hypersensitivity or allergies to vedolizumab or any of its excipients.
4. Subjects who have received either (1) an investigational biologic (other than those listed in Exclusion Criterion #1) within 60 days or 5 half-lives before screening (whichever is longer); or (2) an approved biologic or biosimilar agent within 2 weeks before the first dose of study drug or at any time during the screening period.
5. Subjects with active cerebral/meningeal disease, signs/symptoms or history of progressive multifocal leukoencephalopathy (PML) or any other major neurological disorders including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease.
6. Subjects who currently require surgical intervention or are anticipated to require surgical intervention for UC during this study.
7. Subjects who have had subtotal or total colectomy or have a jejunostomy, ileostomy, colostomy, ileo-anal pouch, or known fixed stenosis of the intestine.
8. Subjects with a current diagnosis of indeterminate colitis.
9. Subjects with clinical features suggesting monogenic very early onset IBD.
10. The subject has other serious comorbidities that will limit his or her ability to complete the study.

Endpoints and Assessments:

Primary Endpoint:

The primary endpoint is clinical remission at Week 54, where clinical remission based on the modified Mayo score is defined as:

- Stool frequency subscore 0 to 1 and a decrease of 1 or more from baseline;
- Rectal bleeding subscore of 0; and,
- Endoscopy subscore 0 to 1 (modified so that a score of 1 does not include friability).

Secondary Endpoints:

Secondary endpoints include:

- Clinical remission at Week 14, where a subject achieves clinical remission if he or she meets the definition described in the primary endpoint.
- Sustained clinical remission at Week 54, where a subject achieves sustained clinical remission if he or she achieved clinical remission (as defined by primary endpoint) at Week 14 and at Week 54.
- Sustained endoscopic remission, defined as Mayo endoscopic score (MES) of ≤1 point, at Week 14 and at Week 54.
- Endoscopic response, defined as a decrease in MES ≥1 point at Week 14.
- Endoscopic response, defined as a decrease in MES ≥1 point at Week 54.
- Corticosteroid-free clinical remission at Week 54, where a subject achieves corticosteroid-free clinical remission at Week 54 if he or she meets the definition described in the primary endpoint and was off corticosteroids at least 12 weeks before Week 54.
- Clinical remission based on complete Mayo score at Week 54, where a subject achieves clinical remission if he or she achieved a complete Mayo score ≤2 points with no individual subscore >1 at Week 54.
- Serum trough concentrations of vedolizumab over time.
- Positive antivedolizumab antibodies (AVAs) and positive neutralizing AVA during the study.
- Sustained clinical response of subjects at Weeks 14 and 54, where a subject meets clinical response if he or she has a reduction in complete Mayo score (see Appendix I) of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.

- Clinical response at Weeks 2, 6, 10, 14, 22, 30, 38, 46, and 54, where a subject achieves clinical response if he or she meets the following definition:
  - Reduction of ≥2 points and ≥25% from the baseline partial Mayo score, including a ≥1-point decrease in the Mayo stool frequency subscore and a ≥1-point reduction in the rectal bleeding subscore or absolute rectal bleeding subscore of ≤1 point.
- Clinical remission at Weeks 2, 6, 10, 14, 22, 30, 38, 46, and 54, where a subject achieves clinical remission based on partial Mayo score (a partial Mayo score of ≤2 points and no individual subscore >1 point).
- Safety assessments: descriptions of adverse events (AEs); SAEs; and adverse events of special interest (AESIs), including evaluation of opportunistic infection, such as PML, liver injury, malignancies, infusion-related reactions, and hypersensitivity.
- Change from baseline in weight gain and linear growth z-score during the course of dosing with vedolizumab.
- Change in Tanner stage at Week 54 compared with baseline, each domain separately.

Exploratory Endpoints:

Exploratory endpoints include:

- Change from baseline in CRP, albumin, and fecal calprotectin by visit.
- Change from baseline in IMPACT-III total and subscale scores at Weeks 14 and 54 for subjects aged 9 to 17 years at the time of the first dose.
- Change from baseline in Mayo and PUCAI scores and subscores by visit.
- Clinical remission based on PUCAI score at Week 54, where a subject achieves clinical remission if he or she has a PUCAI of <10 at Week 54.
- Clinical response based on PUCAI defined as a ≥20-point decrease from baseline in the PUCAI score for Weeks 2, 6, 10, 14, 22, 30, 38, 46, and 54.

Safety: AEs, SAEs, AESIs (infections including opportunistic infection, such as PML, liver injury, malignancies, infusion-related or injection site reactions, and hypersensitivity), vital signs, results of standard laboratory tests (clinical chemistry, hematology, and urine pregnancy test), and AVA titer.

Statistical Considerations:

The PK exposure and response from each planned dose (ie, high dose, low dose) are expected to be similar across the 3 weight categories (≥30 kg; >15 to <30 kg; 10 to 15 kg). In other words, the high dose in the ≥30 kg weight group is expected to have similar effect as the high dose in the >15 to 30 kg and the 10 to 15 kg weight group. Similarly, the low dose within each weight category (≥30 kg; >15 to <30 kg; 10 to 15 kg) is expected to have similar effect. Therefore, the data across the 3 weight categories (≥30 kg; >15 to <30 kg; 10 to 15 kg) within each dose category (high dose, low dose) will be combined and analyzed by dose (high dose, low dose), unless otherwise specified. All the planned analyses will be stratified by dose arm only unless otherwise specified. The primary statistical objective in the efficacy analyses is the estimation of endpoints of interest. No formal hypothesis testing will be performed.

Primary Endpoint Analysis

For the primary endpoint, clinical remission at Week 54, the point estimate of the clinical remission rate and the associated 95% Pearson-Clopper CIs will be presented by dose groups (high dose, low dose).

Secondary Efficacy Analysis

The proportion-based secondary efficacy endpoints are:

- Clinical remission at Week 14.
- Sustained clinical remission at Weeks 14 and 54.
- Sustained endoscopic remission at Weeks 14 and 54.
- Endoscopic response at Week 14.
- Endoscopic response at Week 54.
- Corticosteroid-free clinical remission at Week 54.

- Clinical remission based on complete Mayo score at Week 54.
- Clinical response at Weeks 2, 6, 10, 14, 22, 30, 38, 46, and 54.
- Clinical remission at Weeks 2, 6, 10, 14, 22, 30, 38, 46, and 54.
- Sustained clinical response of subjects at Weeks 14 and 54.

All proportion-based secondary efficacy endpoints will be analyzed similarly as done for the primary endpoint.

The continuous based secondary efficacy endpoints are:

- Change from baseline in weight gain and linear growth z-score during the course of dosing with vedolizumab.

For continuous endpoints, descriptive statistics (non-missing values, mean, median, standard deviation, minimum, and maximum) and corresponding 95% CIs where applicable will be summarized by dose groups (high dose, low dose).

Shift analysis of Tanner stage will be performed at Week 54 compared with baseline, each domain separately.

The subjects' overall AVA status (negative, positive) and proportion of subjects with any positive neutralizing AVA during the study will be summarized. Furthermore, the AVA status (negative, positive) by study visit will be summarized.

Subgroup Analysis

For both the induction and maintenance periods, subgroup analysis will also be performed, replicating the primary analysis, in each of the 3 weight categories (≥30 kg; >15 to <30 kg; 10 to 15 kg).

A subject missing any component of a scale will be considered a nonresponder/nonremitter for that particular endpoint, scale, or time point in the analysis. Moreover, a subject who had dose escalation from low to high dose or who received corticosteroids during the maintenance phase will be considered a nonresponder/nonremitter for that particular endpoint, scale, or time point in the analysis.

Exploratory Endpoints

- Change from baseline in CRP, albumin, and fecal calprotectin by visit.
- Change from baseline in IMPACT-III total and subscale scores at Weeks 14 and 54 for subjects aged 9 to 17 years at the time of the first dose.
- Change from baseline in Mayo and PUCAI scores and subscores by visit.
- Clinical remission based on PUCAI score at Week 54.
- Clinical response based on PUCAI for Weeks 2, 6, 10, 14, 22, 30, 38, 46, and 54.

Exploratory continuous endpoints will be summarized descriptively similar to the continuous secondary endpoints.

Safety Analysis

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 count and proportion of subjects with TEAEs, AESIs, AEs leading to discontinuation, and treatment-emergent SAEs 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 TEAEs overall and by severity. Exposure-adjusted incidence rates will also be analyzed.

PK Analysis

All PK parameters will be summarized using descriptive statistics by dose arm (if applicable) and weight group. Exposure-response analysis in pediatric subjects will be performed as appropriate. Further details will be provided in the SAP. Population PK will be performed if data allow. These analyses will be included in a separate report.

Sample Size Justification:

The primary statistical objective is the estimation of the primary endpoint, clinical remission at Week 54, by dose groups (high dose, low dose). No formal hypothesis testing is planned. The sample-size justification was based on ensuring adequate precision (using the half-width of the 95% CI) for the estimate of the true clinical remission rate.

Assuming the true clinical remission rate of 42% at Week 54, a sample size of 36 subjects in each maintenance arm will provide a 95% Clopper-Pearson exact CI with a lower bound of 25.5% and an upper bound of 59.2%. In addition, the table below summarizes the 95% Clopper-Pearson exact CI for the clinical remission rates ranging from 37% to 47% with a sample size of 36 subjects.

Observed Remission Rates With Clopper-Pearson 95% CI (for N = 36 subjects)

Observed Rate	95% Clopper-Pearson CI
37%	(20.8%-53.8%)
42%	(25.5%-59.2%)
47%	(27.9%-61.9%)

The width of this CI provides adequate precision around the primary endpoint of interest.

To ensure a randomized sample size of 72 subjects (36 per maintenance arm) during the maintenance phase, approximately 120 subjects will need to be enrolled in the 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 interest 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 investigator and subinvestigator should be declared on their curriculum vitae, which must be provided to the sponsor before the start of 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 supplier list in the study manual. The identified vendors will perform these activities either in full or in partnership with the sponsor.

3.2 Coordinating Investigator

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

3.3 List of Abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AVA	antivedolizumab antibody
AxMP	auxiliary medicinal product
AZA	azathioprine
bpm	beats per minute
CD	Crohn's disease
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CSR	clinical study report
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
ET	early termination
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HLT	High Level Term
IA	interim analysis
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
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive web response technology

ITT	intent-to-treat
IV	intravenous
LFT	liver function test
LTFU	long-term follow-up
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
MES	Mayo endoscopic score
mITT	modified intent-to-treat
MTX	methotrexate
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PGA	Physician's Global Assessment
PIBD	pediatric inflammatory bowel disease
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PPS	per-protocol set
PTE	pretreatment event
PUCAI	Pediatric Ulcerative Colitis Activity Index
Q4W	once every 4 weeks
Q8W	once every 8 weeks
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SC	subcutaneous
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAEs	treatment-emergent adverse events
TNF-α	tumor necrosis factor-alpha
UC	ulcerative colitis
ULN	upper limit of normal

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	A reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.
Clinical response based on modified Mayo score	A reduction in modified Mayo score of ≥2 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.
Clinical response based on partial Mayo score	A reduction of ≥2 points and ≥25% from the baseline partial Mayo score, including a ≥1-point decrease in the Mayo stool frequency subscore and a ≥1-point reduction in the rectal bleeding subscore or absolute rectal bleeding subscore of ≤1 point.
Clinical remission based on complete Mayo score	A complete Mayo score (inclusive of physician global assessment) of ≤2 points with no individual subscore >1.
Clinical remission based on modified Mayo score	A modified Mayo score with stool frequency subscore 0 to 1 and a decrease of 1 or more from baseline; rectal bleeding subscore of 0; and endoscopy subscore 0 to 1 (modified so that a score of 1 does not include friability); excludes physician global assessment.
Clinical response based on Pediatric Ulcerative Colitis Activity Index (PUCAI)	A ≥20-point decrease from baseline in PUCAI score.
Clinical remission based on PUCAI	PUCAI score <10.
Endoscopic response	A decrease in Mayo endoscopic score (MES) ≥1 point.
Endoscopic remission	MES of ≤1 point.
Lack of maintenance of clinical response and disease worsening	Defined as the following, at 2 consecutive visits at least 7 days apart: Increase in the Mayo subscore of stool frequency by 1 point to at least ≥2 points, and Increase in the Mayo subscore of rectal bleeding by at least 1 point with an absolute bleeding subscore of ≥2 points.
Treatment-emergent Adverse Events (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).
Study start	Defined as the date of the first subject screened in the study.
End of study	The end of study is defined as last subject, last visit (inclusive of the 18-week post–last-dose follow-up safety visit).
Enrollment	A 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, having satisfied all entry criteria. • Subject takes part in any study activity after screening.

4.0 INTRODUCTION

4.1 Background

4.1.1 Epidemiology of Ulcerative Colitis in the Pediatric Population

In a recent analysis of 2 large United States claims databases, the prevalence of pediatric inflammatory bowel disease (PIBD) (age 2 to 17 years, inclusive) overall increased by 133% from 33.0 cases per 100,000 in 2007 to 77.0 per 100,000 in 2016 (Ye et al. 2019). The annual percentage change in prevalence between 2007 and 2016 was 9.9% (95% CI 9.2-10.5). From 2007 to 2016 ulcerative colitis (UC) prevalence increased from 8.6% to 21.6%, a 152% increase. The overall prevalence of UC in the adult and pediatric population is approximately 200 cases per 100,000 persons in the United States and about 150 cases per 100,000 persons in Western Europe (Loftus et al. 2007; Molodecky et al. 2012; Shivananda et al. 1996; Trallori et al. 1996). With the growing incidence of PIBD, Europe (23 per 100,000 person-years) and North America (15.2 per 100,000 person-years) have the highest PIBD burden. The highest annual incidences of UC were 15.0 per 100,000 in Europe and 10.6 per 100,000 in North America.

Current epidemiology studies of the prevalence of PIBD in different age groups suggest that less than 20% of children with UC and Crohn's disease (CD) are under 10 years of age and most of them weigh less than 30 kg. Thus, the vast majority of the children with PIBD who may benefit from treatment with vedolizumab will weigh more than 30 kg at the time of the need for an alternative to the current standard of care (SOC) (Shavit-Brunschwig et al. 2019).

4.1.2 Clinical Manifestations and Prognosis of UC Pediatric Patients

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).

Treatment options for adult and pediatric patients are similar. Pharmacological treatments for UC include 5-aminosalicylic acid (5-ASA) and its derivatives, corticosteroids, and immunomodulators (thiopurines, such as azathioprine [AZA] and 6-mercaptopurine [6-MP]). 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 moderate to severe pediatric UC (Kader et al. 1999). Over the past decade, tumor necrosis factor-alpha (TNF-α) antagonist therapies have been studied and approved for use in the pediatric population. Infliximab and adalimumab have been approved for use in pediatric patients with moderately to severely active UC in the United States and European Union (EU).

4.1.3 Vedolizumab Intravenous

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 gastrointestinal (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 adult dose and administration regimen consists of 300 mg vedolizumab IV infused intravenously (IV), over approximately 30 minutes, at Day 1 and Weeks 2 and 6 and then once every 8 weeks (Q8W) thereafter. In some regions, once every 4 weeks (Q4W) is also approved in those patients who lose response to Q8W.

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 and pigs, no evidence of significant adverse local effects was seen following administration of vedolizumab IV or vedolizumab subcutaneous (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 in humans.

A 13-week toxicity study of vedolizumab IV in juvenile cynomolgus monkeys (aged 11-15 months at study start) supports studies in the pediatric population down to 2 years of age. Monkeys of this species typically are weaned at approximately 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 (aged approximately 3-7 years): 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. In adults, vedolizumab serum concentrations generally fell in a biexponential fashion until approximately 1 to 10 µg/mL, with a total clearance after IV administration of approximately 0.157 L/day and a serum half-life of approximately 25 days. Thereafter, the serum concentrations fell in a nonlinear fashion. The volume of distribution for vedolizumab IV is approximately 5 L.

In the pivotal phase 3 studies (C13006 and C13007) and Study 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) have been related to exacerbations or complications of the underlying UC or CD. Overall, the safety profile following long-term treatment with vedolizumab IV Q4W or Q8W in Study C13008 for up to 8 years and 16 weeks was consistent with safety in the 52-week studies. 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.

Completed phase 2 pediatric vedolizumab IV Study MLN0002-2003 evaluated treatment with vedolizumab IV through Week 14. Treatment with 150 mg and 300 mg IV doses (≥30 kg weight group) and 100 mg 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, anemia, 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-2005, a long-term safety extension study that enrolled subjects who achieved a clinical response in MLN0002-2003, is currently active.

A reanalysis of serum samples from Studies C13006 and C13007 using a drug-tolerant electrochemiluminescence (ECL) assay showed that 6% (86 of 1434) of subjects who received

vedolizumab in the induction and maintenance phases were found to have positive antivedolizumab antibody (AVA) titers at any time during or after study treatment. Of the 86 AVA-positive subjects, 66 were transiently positive (77%), 20 were persistently positive (23%), and 56 developed neutralizing antibodies (65%). At Week 66, which is approximately 5 half-lives after the last dose of drug received by these subjects, there were 45 of 310 subjects (15%) who were AVA positive.

In the combined vedolizumab population who received IV treatment continuously during the maintenance phase of the parent studies and were enrolled in Study C13008, the number of subjects who were AVA positive at any time during the studies (C13006, C13007, and C13008) was 28 (3%), of which 9 subjects were persistently positive and 17 were demonstrated to be neutralizing. The vedolizumab immunogenicity rate for subjects who were randomized to placebo after receiving 2 doses of vedolizumab was 2% (2 of 119). Development of AVA did not have an impact on safety following IV administration.

The low prevalence of AVA in vedolizumab IV-treated subjects precluded conclusions regarding the potential impact of AVA positivity on efficacy. However, in vedolizumab SC-treated adult subjects (Study MLN0002SC-3031), the development of persistent AVA was associated with a decrease in vedolizumab serum concentrations. The development of AVA and neutralizing antibodies had the potential to have an impact on efficacy.

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 from postmarketing data.

An analysis of off-label use in the pediatric population did not reveal any new safety concerns; 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 safety data are consistent with the safety profile observed in the clinical studies. The benefit-risk profile continues to be positive.

4.2 Rationale for the Proposed Study

Vedolizumab IV has demonstrated statistically significant and clinically relevant evidence of effectiveness in multiple completed clinical studies in adult subjects with moderately to severely active UC. Since vedolizumab's approval for adults, off-label use in pediatric patients with inflammatory bowel disease (IBD) has persisted. Clinical trial results for induction and maintenance vedolizumab treatment are needed to affirm proper dosing, exposure, efficacy, and safety for use of vedolizumab in pediatric patients. Subsequent to results of the MLN002-2003 phase 2 pediatric study, confirmatory results from a phase 3 pediatric study, if positive, would enable the registration of vedolizumab for pediatric patients with IBD and accordingly provide patients benefit from appropriate access to another medical therapeutic option. The data from this study will be used for partial extrapolation of efficacy from adults to pediatric subjects based on the efficacy, safety, and PK data from completed studies in adult subjects.

4.3 Rationale for Auxiliary Medicinal Products for Rescue Treatment

Corticosteroids (eg, prednisone or its equivalent) may be utilized as auxiliary medicinal products (AxMPs) for rescue treatment during the maintenance period of the study. Lack of maintenance of clinical response and worsening of disease during the maintenance period will result in a subject becoming eligible to receive rescue therapy with corticosteroids at the investigator's discretion in an attempt to re-establish response/remission. For details on corticosteroid rescue treatment, see Section 7.3.1.1.2. For an overview on the AxMPs, please see Appendix B.

4.4 Benefit-Risk Profile of Vedolizumab

There remains an unmet medical need in pediatric patients who do not respond, or who lose response, to existing therapy (including conventional therapy or TNF-α antagonists), or in whom side effects of these agents are intolerable or life threatening. Vedolizumab IV may provide an alternative therapy for this patient population.

Vedolizumab IV has demonstrated statistically significant and clinically relevant evidence of effectiveness in multiple completed clinical studies in adult subjects with moderately to severely active UC. In Study MLN0002-2003, similar clinical responses were observed in pediatric subjects with UC, as compared with those seen in adults in previous phase 3 studies of vedolizumab IV induction therapy.

In clinical studies, vedolizumab IV has shown an acceptable and consistent safety profile in adults (≥18 years of age) with body weights ranging from 28.7 kg to 170 kg. In the pivotal phase 3 studies in adult UC subjects (C13006), 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. 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, based on available clinical and postmarketing data, the benefit-risk profile in pediatric subjects with UC is expected to be positive. Further information on vedolizumab is provided in the current edition of the investigator’s brochure.

4.5 Risks Associated With AxMPs

The AxMP class of corticosteroids (eg, prednisone or its equivalent) has potential application for rescue treatment during the maintenance period of this study. Corticosteroids have wide use in the gastroenterology setting as the treatment to control acute disease that has not responded to current therapy. Oral corticosteroids are outlined as a treatment option for acute disease in the Joint European Crohn’s and Colitis Organization and European Society of Pediatric

Gastroenterology, Hepatology and Nutrition evidence-based consensus guidelines on the medical management of pediatric UC (Turner et al. 2012).

Potential side effects of corticosteroid use include, but are not limited to, the following: fluid retention, mood changes, insomnia, hypertension, hyperglycemia, increased susceptibility to infections, osteoporosis and increased risk of fractures, muscle weakness, peptic ulcer with possible subsequent perforation, impaired wound healing, convulsions, menstrual irregularities, posterior subcapsular cataracts, and weight gain. Many of these side effects are only observed with chronic use and are unlikely to present with the short-term use associated with rescue treatment. Additional side effects to consider in children are adrenal suppression and growth retardation with long-term use.

4.6 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

The primary objective of this study is to evaluate the efficacy of 2 different dose regimens of vedolizumab IV in pediatric subjects with moderately to severely active UC during maintenance therapy, based on clinical remission at Week 54.

5.1.2 Secondary Objectives

Secondary objectives of this study are to evaluate:

- The efficacy of high and low doses of vedolizumab IV in pediatric subjects with moderately to severely active UC, based on clinical remission at Week 14.
- The efficacy of high and low doses of vedolizumab IV as measured by sustained clinical remission at Weeks 14 and 54.
- The efficacy of high and low doses of vedolizumab IV as measured by sustained clinical response at Weeks 14 and 54.

- The efficacy of high and low doses of vedolizumab IV as measured by sustained endoscopic remission at Weeks 14 and 54.
- The efficacy of high and low doses of vedolizumab IV as measured by endoscopic response at Weeks 14 and 54.
- The effect of high and low doses of vedolizumab IV on achieving corticosteroid-free remission at Week 54.
- The effect of high and low doses of vedolizumab IV on clinical response over time up to Week 54.
- The efficacy of high and low doses of vedolizumab IV as measured by clinical remission over time up to Week 54.
- Vedolizumab PK in pediatric subjects with moderately to severely active UC after IV administration.
- Safety in pediatric subjects on maintenance therapy up to Week 54.
- The immunogenicity of vedolizumab in pediatric subjects with moderately to severely active UC treated with vedolizumab IV.
- The effect of vedolizumab on patterns of growth and pubertal development in pediatric subjects with moderately to severely active UC during their participation in the study.

5.1.3 Exploratory Objectives

Exploratory objectives of this study are to:

- Explore the relationship between vedolizumab exposure and the clinical and endoscopic response in pediatric subjects treated with vedolizumab IV during both induction and maintenance therapy.
- Assess markers of intestinal inflammation (C-reactive protein [CRP], serum albumin, fecal calprotectin) and analyze their correlation with trough PK levels of vedolizumab.
- Evaluate the quality of life in subjects aged 9 to 17 years who were treated with vedolizumab IV using the IMPACT-III questionnaire.
- Evaluate the efficacy of high and low doses of vedolizumab IV as measured by clinical remission based on Pediatric Ulcerative Colitis Activity Index (PUCAI).
- Evaluate the efficacy of high and low doses of vedolizumab IV as measured by clinical response based on PUCAI.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is clinical remission at Week 54, where clinical remission based on the modified Mayo score is defined as:

- Stool frequency subscore 0 to 1 and a decrease of 1 or more from baseline.
- Rectal bleeding subscore of 0.
- Endoscopy subscore 0 to 1 (modified so that a score of 1 does not include friability).

5.2.2 Secondary Endpoints

Secondary endpoints include:

- Clinical remission at Week 14, where a subject achieves clinical remission if he or she meets the definition described in the primary endpoint.
- Sustained clinical remission at Week 54, where a subject achieves sustained clinical remission if he or she achieved clinical remission (as defined by primary endpoint) at Week 14 and at Week 54.
- Sustained endoscopic remission, defined as Mayo endoscopic score (MES) of ≤1 point, at Week 14 and at Week 54.
- Endoscopic response, defined as a decrease in MES ≥1 point at Week 14.
- Endoscopic response, defined as a decrease in MES ≥1 point at Week 54.
- Corticosteroid-free clinical remission at Week 54, where a subject achieves corticosteroid-free clinical remission at Week 54 if he or she meets the definition described in the primary endpoint and was off corticosteroids at least 12 weeks prior to and at Week 54.
- Clinical remission based on complete Mayo score at Week 54, where a subject achieves clinical remission if he or she achieved a complete Mayo score ≤2 points with no individual subscore >1 at Week 54.
- Serum trough concentrations of vedolizumab over time.
- Positive AVA and positive neutralizing AVA during the study.
- Sustained clinical response of subjects at Weeks 14 and 54, where a subject meets clinical response if he or she has a reduction in complete Mayo score (see Appendix I) of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.

- Clinical response at Weeks 2, 6, 10, 14, 22, 30, 38, 46, and 54, where a subject achieves clinical response if he or she meets the following definition:
  - Reduction of ≥2 points and ≥25% from the baseline partial Mayo score, including a ≥1-point decrease in the Mayo stool frequency subscore and a ≥1-point reduction in the rectal bleeding subscore or absolute rectal bleeding subscore of ≤1 point.
- Clinical remission at Weeks 2, 6, 10, 14, 22, 30, 38, 46, and 54, where a subject achieves clinical remission based on partial Mayo score (a partial Mayo score of ≤2 points and no individual subscore >1 point).
- Safety assessments: descriptions of AEs; SAEs; and adverse events of special interest (AESIs), including evaluation of opportunistic infection, such as progressive multifocal leukoencephalopathy (PML), liver injury, malignancies, infusion-related reactions, and hypersensitivity.
- Change from baseline in weight gain and linear growth z-score during the course of dosing with vedolizumab.
- Change in Tanner stage at Week 54 compared with baseline, each domain separately.

5.2.3 Exploratory Endpoints

Exploratory endpoints include:

- Change from baseline in CRP, albumin, and fecal calprotectin by visit.
- Change from baseline in IMPACT-III total and subscale scores at Weeks 14 and 54 for subjects aged 9 to 17 years at the time of the first dose.
- Change from baseline in Mayo and PUCAI scores and subscores by visit.
- Clinical remission based on PUCAI score at Week 54, where a subject achieves clinical remission if he or she has a PUCAI of <10 at Week 54.
- Clinical response based on PUCAI defined as a ≥20-point decrease from baseline in the PUCAI score for Weeks 2, 6, 10, 14, 22, 30, 38, 46, and 54.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 3 study of vedolizumab administered during a 14-week, open-label induction period followed by a 40-week, 2-dose arm, randomized, double-blind maintenance period designed to evaluate the efficacy, safety, PK, and immunogenicity of high and low doses in 3 different weight groups of vedolizumab IV for maintenance of remission in children aged 2 to 17 years, inclusive, who weigh ≥10 kg with moderately to severely active UC. The data from this study will be used for partial extrapolation of efficacy from adults to pediatric subjects based on the efficacy, safety, and PK data from completed studies in adult subjects.

Screening: Subjects must have been diagnosed with moderately to severely active UC at least 1 month before screening and failed response to, lost response to, or been intolerant to at least 1 of the current SOC induction and maintenance therapies for UC, including immunomodulators (eg, AZA, 6-MP, methotrexate [MTX]), and TNF-α antagonists (eg, infliximab, adalimumab). Lack of response to corticosteroids at the time of the initial diagnosis of UC or inability to wean off corticosteroids without a recurrence of symptoms will also qualify a subject for the study. Subjects or their legally authorized representative (or adult caregivers) will be provided with an electronic symptom diary and trained on its use during the initial screening visit and will complete the symptom diary daily throughout participation in the study. Subjects will be evaluated during a 35-day screening period by using symptom diaries, colonoscopy, and determination of fecal calprotectin and CRP. Those with moderately to severely active UC, defined by a modified Mayo score (see Appendix I and Appendix L) of 5 to 9 (sum of the stool frequency, rectal bleeding, and endoscopic subscores with an endoscopic subscore of ≥2) (and meeting all other eligibility criteria), can enter the open-label induction period. The PUCAI will also be assessed (see Appendix J and Appendix L). All colonoscopies (at screening and all subsequent flexible sigmoidoscopies at Weeks 14 and 54 or the early termination [ET] visit) will be centrally read for Mayo endoscopic subscore. Historical colonoscopy (with recorded video) done up to 30 days prior to signing of assent/informed consent, can be submitted to central readers for assessment after assent/informed consent is obtained. If found to be adequate by central readers, this video colonoscopy will be used for the assessment of Mayo endoscopic subscore, which can be used as the baseline assessment.

Induction Period: On Day 1, the modified Mayo score should be verified and documented before infusion. During the induction period, subjects ≥30 kg will receive open-label vedolizumab, 300 mg IV at Day 1, Week 2, and Week 6; subjects who weigh >15 to <30 kg will receive an open-label dose of vedolizumab 200 mg IV at Day 1, Week 2, and Week 6; and subjects who weigh 10 to 15 kg will receive an open-label dose of vedolizumab 150 mg IV at Day 1, Week 2, and Week 6. These doses were determined using an established population PK model, developed using data from adult phase 3 studies and the pediatric phase 2 study (MLN0002-2003) for ≥30 kg and <30 kg cohorts, to match the vedolizumab exposure seen in the adult populations during the induction phase. Approximately 120 subjects will be enrolled in the induction period with around three-fourths of subjects weighing ≥30 kg and around one-fourth of subjects weighing 10 to <30 kg at the time of enrollment into the study.

Weight Group [a]	Induction Dose
Subjects ≥30 kg	300 mg IV at Day 1, Week 2 and Week 6
Subjects >15 to <30 kg	200 mg IV at Day 1, Week 2 and Week 6
Subjects 10 to 15 kg	150 mg IV at Day 1, Week 2 and Week 6

IV: intravenous.

[a] No change in induction dose for weight change over time.

At Week 14, all subjects will be evaluated for clinical response, based on modified Mayo score (defined as a reduction of ≥2 points and ≥30% from the baseline modified Mayo score with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point). Those who do not achieve a clinical response during the open-label induction period will discontinue from the study, complete the end-of-study (EOS)/ET visit, and proceed to the follow-up safety assessment 18 weeks after their last dose of study drug. These subjects will then enter Study MLN0002-3029 for an observational long-term follow-up (LTFU) period of 2 years after the last dose of study drug. During the LTFU period, data will be collected either by clinic visit OR, if site attendance is not feasible, by phone call every 6 months.

Randomization Into the Maintenance Period: At Week 14, those who achieve clinical response (defined as a reduction of ≥2 points and ≥30% from the baseline modified Mayo score with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point) will be stratified by previous exposure/failure to TNF-α antagonists therapy or naive to TNF-α antagonists therapy, and by weight group (≥30 kg; >15 kg to <30 kg; 10 kg to 15 kg). Subjects will be randomized 1:1 to one of the 2 dose groups (high dose, low dose), within each of the 3 weight groups (≥30 kg; >15 to <30 kg; 10 to 15 kg), for the double-blind maintenance period.

Weight Group [a]	High Dose	Low Dose
Subjects ≥30 kg	300 mg IV Q8W	150 mg IV Q8W
Subjects >15 to <30 kg	200 mg IV Q8W	100 mg IV Q8W
Subjects 10 to 15 kg	150 mg IV Q8W	100 mg IV Q8W

IV: intravenous; Q8W: once every 8 weeks.

[a] During the maintenance period, adjustments to the dose will be as described for lack of maintenance of clinical response and worsening of disease only; no adjustments made strictly on the basis of weight change over time.

Maintenance Period: Subjects who qualify as responders at the end of the induction period (Week 14) will initiate blinded IV doses of vedolizumab Q8W as maintenance dose through Week 46. The maintenance doses for the 3 weight groups were chosen similar to the way induction doses were chosen. A population PK model was used to match the vedolizumab exposure seen in phase 3 studies for the adult population during the maintenance phase. The high and low doses were selected to maximize the dose difference between the 2 arms while maintaining the exposure within the adult population range. Based on the chosen induction dose, high and low maintenance doses of 300 mg and 150 mg were chosen for the ≥30 kg weight group, 200 mg and 100 mg were chosen for the >15 to <30 kg weight group, and 150 mg and 100 mg were chosen for the 10 to 15 kg weight group. A 150 mg high maintenance dose in the 10 to 15 kg weight group was predicted to result in an exposure closer to, but not exceeding, the upper limit of the adult exposure in the maintenance phase. Similarly, a 100 mg low maintenance dose was predicted to result in an exposure closer to, but not below, the lower limit of adult exposure in the maintenance phase. A 100 mg low maintenance dose was predicted to result in similar and consistent exposure among the entire <30 kg weight groups. A dose of 75 mg was considered for the low maintenance dose in the 10 to 15 kg weight cohort; however, this was predicted to have resulted in an exposure less than adult phase 3 exposure.

At each visit before the infusion, clinical response based on partial Mayo score will be assessed. Improvement or maintenance of clinical response will result in continuation of the blinded dosing of vedolizumab IV. Lack of maintenance of clinical response and **worsening of disease** are defined as the following at 2 consecutive visits (scheduled or unscheduled) at least 7 days apart:

- Increase in the Mayo subscore of stool frequency by 1 point to at least ≥2 points; and
- Increase in the Mayo subscore of rectal bleeding by at least 1 point with an absolute bleeding subscore of ≥2 points.

In addition to safety assessment and evaluation of symptoms and laboratory parameters indicative of disease activity at the applicable visits, an endoscopy will be performed at Week 54 to evaluate endoscopic response and remission. Blood samples will be collected for vedolizumab PK and immunogenicity evaluation throughout the study. Subjects who continue to maintain a corticosteroid-free clinical response at Week 54 will be eligible to receive study drug in the MLN0002-3029 extension study.

For subjects who do not maintain corticosteroid-free clinical response at Week 54, or who discontinue study drug at any time during the induction or maintenance periods of this study, final on-study assessments will include an EOS or ET visit and a follow-up safety visit 18 weeks after the last dose of study drug. Subjects will then enter Study MLN0002-3029 for an observational LTFU period of 2 years after the last dose of study drug. During the LTFU period, data will be collected either by clinic visit or, if site attendance is not feasible, will be collected by phone call every 6 months.

Dose Escalation and Steroid Rescue During the Maintenance Period: Lack of maintenance of clinical response and worsening of disease will result in a blinded dose escalation based on the weight at the time of the worsening of disease as described in the table below.

Weight Group (at Time of Randomization Into the Maintenance Period)	Blinded Dose (at Randomization)	Weight Group (at Time of Disease Worsening)	Dose Escalation?	Blinded Dose (After Disease Worsening)
10 to 15 kg	100 mg IV Q8W	10 to 15 kg	Yes	150 mg IV Q8W
		>15 to <30 kg	Yes	200 mg IV Q8W
		≥30 kg	Yes	300 mg IV Q8W
	150 mg IV Q8W	10 to 15 kg	No	150 mg IV Q8W
		>15 to <30 kg	Yes	200 mg IV Q8W
		≥30 kg	Yes	300 mg IV Q8W
>15 to <30 kg	100 mg IV Q8W	10 to 15 kg	Yes	150 mg IV Q8W
		>15 to <30 kg	Yes	200 mg IV Q8W
		≥30 kg	Yes	300 mg IV Q8W
	200 mg IV Q8W	10 to 15 kg	No	200 mg IV Q8W
		>15 to <30 kg	No	200 mg IV Q8W
		≥30 kg	Yes	300 mg IV Q8W

Weight Group (at Time of Randomization Into the Maintenance Period)	Blinded Dose (at Randomization)	Weight Group (at Time of Disease Worsening)	Dose Escalation?	Blinded Dose (After Disease Worsening)
≥30 kg	150 mg IV Q8W	10 to 15 kg	No	150 mg IV Q8W
		>15 to <30 kg	Yes	200 mg IV Q8W
		≥30 kg	Yes	300 mg IV Q8W
	300 mg IV Q8W	10 to 15 kg	No	300 mg IV Q8W
		>15 to <30 kg	No	300 mg IV Q8W
		≥30 kg	No	300 mg IV Q8W

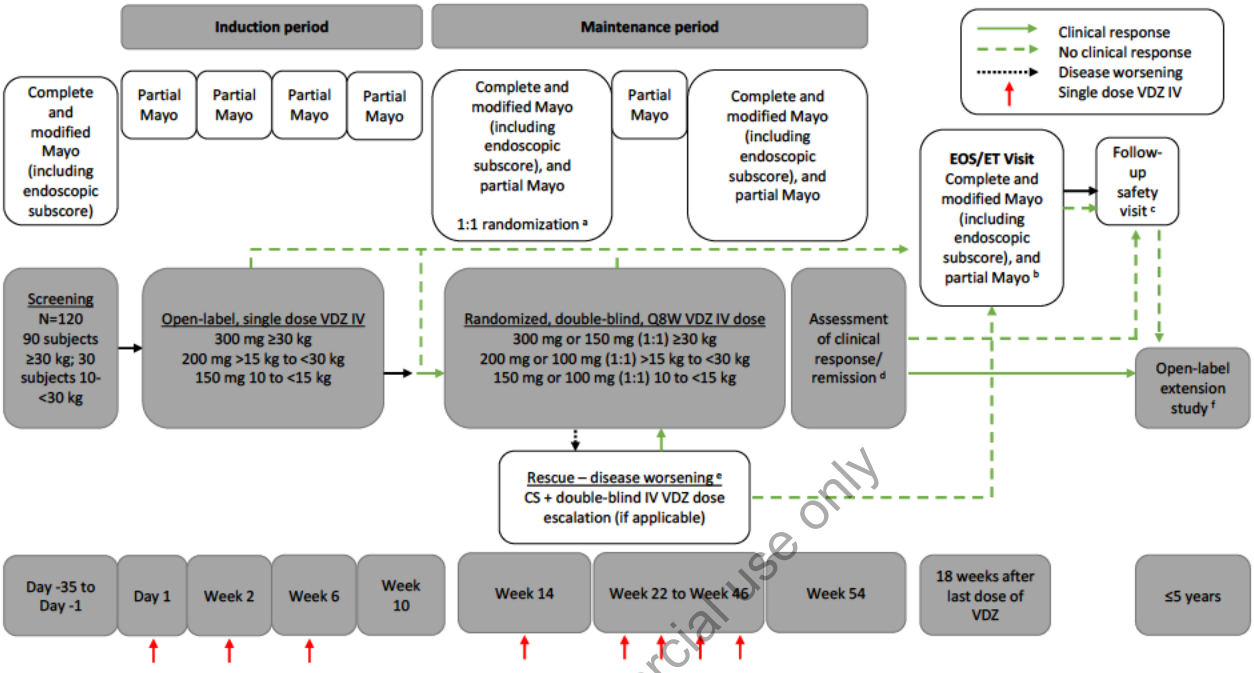
IV: intravenous; Q8W: once every 8 weeks.

Lack of maintenance of clinical response and worsening of disease will also result in subjects who are receiving vedolizumab IV to become eligible to receive rescue therapy with corticosteroids at investigator's discretion in an attempt to re-establish response/remission during the maintenance period. Those subjects whose dose is escalated and/or who receive rescue corticosteroids will, for the analysis of blinded maintenance dose groups, be considered nonresponders to the initial blinded dose of vedolizumab; however, they can remain in the study, and safety, PK, and efficacy data will continue to be assessed in this cohort for the duration of the study. If the investigator elects to continue the subject in the study and initiates corticosteroid rescue at a scheduled or unscheduled visit, it must be based on evaluation of Mayo score with documentation of worsening. Prescribed doses of corticosteroids at the discretion of their investigator should not exceed 40 mg or 1 mg/kg (whichever is lower) of oral prednisone per day or its equivalent. All subjects, including those initiated on corticosteroid rescue therapy, who do not achieve clinical response (as previously defined) in 2 subsequent consecutive visits should be discontinued from the study and proceed to the EOS/ET visit, followed by the follow-up safety visit 18 weeks after their last dose of study drug. These subjects will then enter Study MLN0002-3029 for an observational LTFU period of 2 years after the last dose of study drug. During the LTFU period, data will be collected either by clinic visit or, if site attendance is not feasible, will be collected by phone call every 6 months.

After initiation of corticosteroid rescue therapy, tapering of corticosteroids will start if/when the subject has achieved clinical response based on Mayo score measured at the next scheduled or unscheduled follow-up visit. Corticosteroids will be tapered on a controlled schedule defined in the protocol (see Section 7.3.1.1) designed to wean subjects off corticosteroids within 12 weeks of initiation of tapering. Worsening of disease on tapering of corticosteroids will result in discontinuation from the study; the subject will proceed to the EOS/ET visit followed by the follow-up safety visit 18 weeks after their last dose of study drug. These subjects will enter study MLN0002-3029 for an observational LTFU period of 2 years after the last dose of study drug. During the LTFU period, data will be collected either by clinic visit OR, if site attendance is not feasible, by phone call every 6 months.

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

Figure 6.a Schematic of Study Design



CS: corticosteroid; EOS: end of study; ET: early termination; IV: intravenous; LTFU: long-term follow-up; PK: pharmacokinetics; UC: ulcerative colitis; VDZ: vedolizumab.

[a] At Week 14, subjects who achieve a clinical response will be randomized 1:1 to a double-blind maintenance period starting at Week 14 through Week 54. If no clinical response is achieved by Week 14, the subject will discontinue from the study, proceed to the EOS/ET visit, and a follow-up safety visit 18 weeks after the last dose of study drug and will continue into the extension study for an observational LTFU period of 2 years after the last dose of study drug. During the LTFU period, data will be collected either by clinic visit OR, if site attendance is not feasible, by phone call every 6 months.

[b] If discontinuation during the maintenance phase occurs before or at the time of Week 30 visit, the endoscopy required for the ET visit will be waived.

[c] Final assessment in this study will include a follow-up safety visit 18 weeks after the last dose of study drug for subjects who do not continue into the extension study for continued treatment with vedolizumab and for subjects who discontinue study drug at any time during the study. These subjects will continue into the extension study for an observational LTFU period of 2 years after the last dose of study drug. During the LTFU period, data will be collected either by clinic visit OR, if site attendance is not feasible, by phone call every 6 months.

[d] At Week 54, subjects will undergo flexible sigmoidoscopy in addition to symptom, safety, and laboratory evaluation to fully assess clinical and endoscopic response/remission.

[e] Failure to maintain clinical response and worsening of disease will result in the eligibility of subjects who are receiving vedolizumab IV to receive additional rescue therapy with corticosteroids at investigator discretion in an attempt to re-establish response/remission during the maintenance period. These subjects will be considered nonresponders/nonremitters to the initial blinded dose of vedolizumab; however, safety, PK, and efficacy data will continue to be assessed.

[f] Subjects who continue to maintain a corticosteroid-free clinical response at Week 54 may continue treatment with vedolizumab in the extension study for up to 5 years, or until approval of vedolizumab for children, or cessation of vedolizumab drug development for UC in children (see Section 9.2.5).

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Study Design Rationale

The study design includes an open-label induction phase, with randomized assignment to one of 2 active treatment blinded dose arms (ie, high or low dose) in the maintenance phase. The use of high and low blinded dose arms of vedolizumab IV (the high dose arm continuing the dose used open label during induction and the low dose arm receiving a portion [one-half or two-thirds] of the induction dose, both given Q8W), will allow for evaluation of maintenance of remission, safety, and steady-state PK levels between the 2 dose arms.

6.2.2 Dose Selection Rationale

Given the similarity of disease between adults and children with IBD, a similar response is expected with a similar target vedolizumab exposure. Hence, selection of dose for the induction and maintenance phase was based on matching the adult exposure range.

The approved dosing and administration regimen of vedolizumab for adult patients with IBD is 300 mg vedolizumab IV at Weeks 0, 2, and 6 and then Q8W (in some countries Q4W is allowed for patients who lose response at Q8W). A phase 2, double-blind, randomized, dose-ranging study (MLN0002-2003) was conducted to evaluate vedolizumab PK in pediatric subjects (2 to 17 years of age) with moderately to severely active UC or CD. In addition, the safety profile and the clinical outcomes of vedolizumab treatment were also evaluated. The totality of the data was used to inform the design of the phase 3 studies in pediatric subjects with UC or CD.

A preliminary population PK analysis based on pooled data from adults and pediatric subjects showed that the estimated clearances for pediatric subjects ≥30 kg were within a similar range to those seen in adults previously dosed with vedolizumab 300 mg IV. Also, based on this PK model, simulations of vedolizumab concentrations for pediatric subjects across body weights of 30 kg to 90 kg suggested that the dose of 300 mg would deliver a similar vedolizumab exposure in pediatric subjects ≥30 kg compared to adult subjects from historical studies. The clinical response and remission rates evaluated at Week 14 in Study MLN0002-2003 for pediatric subjects ≥30 kg were comparable with those seen in adult subjects who were evaluated at Week 6 of induction therapy in previous pivotal phase 3 studies. Furthermore, drug-related AEs were similar in both dose arms (300 mg and 150 mg) over 22 weeks of treatment with vedolizumab in MLN0002-2003. Thus, a dose of 300 mg IV has been chosen as the induction dose to be given open label to all subjects ≥30 kg in this phase 3 study. To determine the appropriate maintenance dose of vedolizumab IV for subjects weighing ≥30 kg, 2 blinded dose groups of vedolizumab IV (300 mg IV Q8W and 150 mg IV Q8W) will be studied starting at Week 14.

In the phase 2 study (MLN0002-2003), pediatric subjects 10 to <30 kg were given a 200 mg or 100 mg dose. An interim analysis (IA) of PK data was conducted to inform the induction and maintenance dose selection for the 10 to <30 kg weight cohort in this phase 3 study. Based on the IA, an induction dose of 200 mg in the 10 to 15 kg weight group would have resulted in an exposure greater than the induction exposure in the adult and >30 kg cohort receiving an

induction dose of 300 mg. Hence the <30 kg weight group was divided into 10 to 15 kg weight cohort and >15 to <30 kg weight cohort. The >15 to <30 kg weight cohort retained the induction dose of 200 mg similar to the phase 2 study (MLN0002-2003) to match the induction exposure in the adult and >30 kg cohort, while the induction dose was reevaluated for the 10 to 15 kg weight cohort and determined to be 150 mg. To determine the appropriate maintenance dose of vedolizumab IV for subjects weighing 15 to <30 kg, 2 blinded dose groups for each <30 kg weight group, 150 mg and 100 mg IV Q8W (for 10 to 15 kg weight group) and 200 mg and 100 mg IV Q8W (for >15 to <30 kg weight group), will be studied starting at Week 14.

6.2.3 Endpoint Rationale

Endpoints are consistent and in line with clinical practice:

- Assessing clinical response and remission both at Weeks 14 and 54.
- Safety.
- PK.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known benefit-risk profile for the product, such that the benefit-risk 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 Study Sites

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

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

In the event that the sponsor, an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for ET or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

7.1 Inclusion Criteria

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

1. In the opinion of the investigator, the subject or subject's legally authorized representative, subject's parent, or legal guardian (adult caregiver) is capable of understanding and complying with protocol requirements.
2. The subject, subject's legally authorized representative, or adult caregiver signs and dates a written informed consent and/or pediatric assent form and any required privacy authorization prior to the initiation of any study procedures, as required per local regulations.
3. The subject has moderately to severely active UC, unresponsive or intolerant to their current SOC.
4. The subject is aged 2 to 17 years, inclusive, at the time of screening and enrollment into the maintenance phase of the study.
5. The subject weighs ≥10 kg at the time of screening and enrollment into the study.
6. Subjects with UC diagnosed at least 1 month before screening. Subjects with moderately to severely active UC based on a modified Mayo score of 5 to 9 (sum of Mayo endoscopic subscore, stool frequency subscore, and rectal bleeding subscore) with a Mayo endoscopic subscore of ≥2 (with the presence of mucosal friability excluding an endoscopic subscore of 1 and mandating a score of at least 2) at screening endoscopy.
7. Subjects who have failed, lost response to, or been intolerant to treatment with at least 1 of the following agents: corticosteroids, immunomodulators (eg, AZA, 6-MP, MTX), and/or TNF-α antagonist therapy (eg, infliximab, adalimumab). This includes subjects who are dependent on corticosteroids to control symptoms and who are experiencing worsening of disease in the moderate-to-severe range when attempting to wean off corticosteroids.
8. Subjects with evidence of UC extending proximal to the rectum (ie, not limited to proctitis), at a minimum.
9. Subjects with extensive colitis or pancolitis of >8 years' duration or left-sided colitis of >12 years' duration must have documented evidence of a negative surveillance colonoscopy within 12 months before screening.
10. Subjects with vaccinations that are up-to-date based on the countrywide, accepted schedule of childhood vaccines.
11. A male subject who is sexually active with a female partner of childbearing potential* agrees to use a barrier method of contraception (eg, condom with or without spermicide)* from signing of subject/parental informed consent and/or pediatric assent throughout the duration

of the study and for 18 weeks after last dose. The female partner of a male subject should also be advised to use a highly effective method of contraception.*

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

* Highly effective methods of contraception are defined in Section 9.1.10, and reporting responsibilities are defined in Section 9.1.11.

7.2 Exclusion Criteria

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

1. Subjects who have had previous exposure to approved or investigational anti-integrins including, but not limited to natalizumab, efalizumab, etrolizumab, or AMG 181, or MAdCAM-1 antagonists or rituximab.
2. Subjects who have had prior exposure to vedolizumab.
3. Subjects with hypersensitivity or allergies to vedolizumab or any of its excipients.
4. Subjects who have received either (1) an investigational biologic (other than those listed in Exclusion Criterion #1) within 60 days or 5 half-lives before screening (whichever is longer); or (2) an approved biologic or biosimilar agent within 2 weeks before the first dose of study drug or at any time during the screening period.
5. Subjects with active cerebral/meningeal disease, signs/symptoms or history of PML or any other major neurological disorders including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease.
6. The subject had a clinically significant infection (eg, pneumonia, pyelonephritis, coronavirus disease 2019 [COVID-19]) within 30 days prior to first dose of study drug.
7. The subject has received any live vaccinations within 30 days prior to first dose of study drug.
8. Subjects who currently require surgical intervention or are anticipated to require surgical intervention for UC during this study.
9. Subjects who have had subtotal or total colectomy or have a jejunostomy, ileostomy, colostomy, ileo-anal pouch, or known fixed stenosis of the intestine.
10. Subjects with any unstable or uncontrolled cardiovascular, heart failure moderate to severe (New York Class Association III or IV), pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, neurological, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise subject safety.

11. Subjects with a current diagnosis of indeterminate colitis.
12. Subjects with clinical features suggesting monogenic very early onset IBD.
13. Subject with active or latent tuberculosis (TB), as evidenced by a diagnostic TB test performed within 30 days of screening or during the screening period that is positive, defined as:
    - Positive QuantiFERON test or 2 successive indeterminate QuantiFERON tests, ***OR***
    - A TB skin test reaction ≥5 mm.

    NOTE: If subjects have received Bacillus Calmette–Guérin vaccine, then a QuantiFERON TB Gold test should be performed instead of the TB skin test.

    NOTE: Subjects with documented previously treated TB with a negative QuantiFERON test can be included in the study.
14. Subjects with evidence of positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Hepatitis B virus (HBV) immune subjects (ie, HBsAg-negative and hepatitis B antibody–positive) may, however, be included. Note: If a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if the absence of HBV DNA is confirmed by HBV DNA polymerase chain reaction reflex testing performed in the central laboratory.

    Subjects with chronic hepatitis C virus (HCV) (ie, positive HCV antibody [HCVAb] and HCV RNA). Note: Subjects who are HCVAb–positive without evidence of HCV RNA may be considered eligible (spontaneous viral clearance or previously treated and cured [defined as no evidence of HCV RNA at least 12 weeks before baseline]).
15. The subject has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
16. The subject has, in the judgment of the investigator, clinically significant abnormal hematological parameters of hemoglobin, hematocrit, or erythrocytes at screening.
17. The subject has any of the following laboratory abnormalities during the screening period:
    a) Lymphocyte count $<1.0 \times 10^9$/L or investigator concern regarding underlying lymphocytopenia.
    b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× the upper limit of normal (ULN).
    c) Alkaline phosphatase >3×ULN.
    d) Serum creatinine >2×ULN.
18. The subject has evidence of dysplasia or history of malignancy other than a successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.

19. 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 GI symptoms (eg, abdominal pain) in the opinion of the investigator.
20. Subjects with positive stool studies for ova and/or parasites or stool culture at screening visit.
21. Subjects with positive *Clostridioides difficile (C difficile)* stool test at screening visit.

7.3 Excluded Medications and/or Procedures, and Treatments

The following medications are excluded from use during the study:

- Any treatment for UC other than those listed in Section 7.3.1 (either approved or investigational).
- 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, and menstrual cramps is permitted.)
- TNF-α antagonists may not be administered after signing subject/parental informed consent and/or pediatric assent to participate in the study.
- Topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories may not be administered within 2 weeks of the administration of the first dose of study drug.
- Janus kinase inhibitors, cyclosporine, or tacrolimus may not be administered after signing subject/parental informed consent and/or pediatric assent to participate in the study.

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

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 UC 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

The following medications are permitted during the study:

- Immunomodulators (such as MTX, AZA, 6-MP), stable for at least 8 weeks prior to first dose of study drug.

- Oral 5-ASAs, probiotics, enteral nutrition, or antibiotics for the treatment of UC must be stable for at least 2 weeks prior to first dose of study drug. Antibiotics for other indications must be discussed with the medical monitor.
- Antidiarrheals for control of chronic diarrhea. Any significant increase in the subject's use in the 2 weeks prior to first dose of study drug must be discussed with the medical monitor.

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

Prior to initiating treatment with vedolizumab, all patients should be brought up to date with all recommended immunizations. Patients receiving vedolizumab may receive nonlive vaccines (eg, subunit or inactivated vaccines). There are no data on the secondary transmission of infection by live vaccines in patients receiving vedolizumab. Live vaccines may be administered concurrently with vedolizumab only if the benefits clearly outweigh the risks.

7.3.1.1 Oral Corticosteroid Dosing

7.3.1.1.1 Corticosteroids During Screening and Induction

Corticosteroids should not be initiated during the screening or induction periods. For subjects already on corticosteroids at the time of signing the informed consent (not to exceed 40 mg or 1 mg/kg [whichever is lower] of oral prednisone per day or its equivalent), their dose must remain stable during the last 2 weeks of screening and for at least the first 2 weeks after their initial dose of study drug.

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

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

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

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

By Week 14, tapering of corticosteroids should be initiated for subjects who are eligible to continue in the maintenance period and have not started tapering before Week 14.

7.3.1.1.2 Corticosteroid Rescue Treatment

A one-time rescue with corticosteroids is possible during the maintenance period of this study. The investigator can initiate corticosteroid rescue therapy at a scheduled or unscheduled visit during the maintenance period based on evaluation of Mayo score with documentation of disease worsening as defined in Section 3.5. Note that the prednisone (or equivalent) dosing may not exceed 40 mg per day or 1 mg/kg/day (whichever is lower). Worsening of disease during the induction period will result in discontinuation of the subject.

Tapering of corticosteroids will start if/when the subject has achieved clinical response, as previously defined, with the partial Mayo score measured at the time of the next infusion of vedolizumab after initiation of corticosteroids. Corticosteroids will be tapered on a controlled schedule as described below.

- For subjects receiving a corticosteroid dose of ≥20 mg/day, tapering may resume by 5 mg/week down to 20 mg/day for subjects weighing ≥40 kg and down to 0.5 mg/kg/day for those <40 kg. Once these thresholds are reached, the corticosteroid dose will be held stable until the next dose of study drug is given. Thereafter, continued corticosteroid tapering by 5 mg/week down to 10 mg/day, and thereafter by 2.5 mg/week until zero.
- For subjects receiving a corticosteroid dose of <20 mg/day, tapering may resume by 5 mg/week down to 10 mg/day for those who weigh ≥40 kg or more and down to 0.25 mg/kg/day for those weighing <40 kg. Once these thresholds are reached, the corticosteroid dose will be held stable until the next dose of study drug is given. Thereafter, continued corticosteroid tapering by 2.5 mg/week until zero.

Lack of maintenance of clinical response and worsening of disease upon tapering of corticosteroids will result in discontinuation from the study, and the subject will proceed to the end-of-treatment visit followed by the follow-up safety visit 18 weeks after the last dose of study drug. The subject will then enter Study MLN0002-3029 for an observational LTFU period of 2 years after the last dose of study drug. During the LTFU period, data will be collected either by clinic visit OR, if site attendance is not feasible, by phone call every 6 months.

7.4 Diet, Fluid, and Activity 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

will be collected. For subjects who are screen failures, refer to Section 9.1.21.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE (eg, serious or severe hypersensitivity reaction, such as anaphylaxis, or new onset of malignancy that could interfere with the subject's participation in a clinical study) that requires ET because continued participation imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of the PTE or AE.

   - 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 9.1.9), if the following circumstances occur at any time during study drug treatment:

     – ALT or AST >8× ULN, or

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

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

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

   - Leukopenia or lymphopenia: white blood cell 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 $<1.0 \times 10^9$/L at any point in the study. The absolute lymphocyte count must be repeated at appropriate intervals as determined by the investigator. The next dose of vedolizumab can be administered only if the absolute lymphocyte count is $\geq 1.0 \times 10^9$/L. If the absolute lymphocyte count remains $<1.0 \times 10^9$/L, study drug should be discontinued and the subject withdrawn from the study.

   - PML:

     — Subjects with PML as confirmed by a neurologist or as adjudicated by the PML Independent Adjudication Committee (IAC) will be withdrawn from the study.

   - Any serious infection that meets the following criteria:

     — Life threatening as defined in Section 10.1.4.

     — Requires intensive care unit admission.

     — Systemic opportunistic infection including TB, cytomegalovirus (CMV) (including CMV colitis), and listeriosis.

2. The subject's weight decreases to <10 kg during the study, confirmed at 2 consecutive visits (scheduled or unscheduled) at least 7 days apart.

3. 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.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the electronic case report form (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).
6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Pregnancy. The subject is found to be pregnant.

   NOTE: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.
8. Lack of efficacy. The investigator has determined that the subject is not benefiting from study treatment and continued participation would pose an unacceptable risk to the subject.
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 discontinuation or withdrawal criteria described in Section 7.5 or if the investigator determines that discontinuation of the study drug is in the subject's best interest. In addition, a subject or subject's parent/legal guardian may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for discontinuation or withdrawal must be recorded by the investigator. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. If discontinuation occurs within 2 weeks after a scheduled visit, only assessments pertaining to the EOS visit (and not completed in the most recent scheduled visit) will be required. The investigator may repeat any of the scheduled visit assessments as deemed clinically appropriate. If discontinuation during the maintenance phase occurs before or at the time of the Week 30 visit, the endoscopy required for the ET visit will be waived. Discontinued subjects will enter Study MLN0002-3029 for an observational LTFU period of 2 years after the last dose of study drug. During the LTFU period, data will be collected either by clinic visit OR, if site attendance is not feasible, by phone call every 6 months.

7.6.1 Subjects Who Withdraw From the Study

A subject/subject's legally authorized representative/adult caregiver may withdraw (eg, withdraw assent/consent) from the study at any time for any reason without prejudice to the subject's future medical care by the investigator or at the institution. The investigator or the sponsor may withdraw the subject at any time (eg, in the interest of the subject's safety). The investigator is encouraged to discuss withdrawal of a subject from study treatment with the sponsor's medical monitor when possible.

If a subject/subject's legally authorized representative/adult caregiver withdraws assent/consent during the treatment period, the subject will undergo all ET assessments and procedures as long as the subject/subject's legally authorized representative/adult caregiver agrees to do so. If discontinuation occurs within 2 weeks after a scheduled visit, only assessments pertaining to the ET visit (and not completed in the most recent scheduled visit) will be required. No further follow-up will be conducted after this visit.

If a subject/subject's legally authorized representative/adult caregiver withdraws assent/consent during the follow-up safety period, the subject will undergo the follow-up safety visit assessments and procedures as soon as possible, as long as the subject/subject's legally authorized representative/adult caregiver agrees to do so. No further follow-up will be conducted after this visit.

7.6.2 Subjects Who Discontinue From the Study

Subjects who permanently discontinue study treatment, but do not withdraw assent or whose legally authorized representative/adult caregiver does not withdraw consent, will complete the ET procedures and then the follow-up safety visit 18 weeks after the subject's last dose. If discontinuation occurs within 2 weeks after a scheduled visit, only assessments pertaining to the EOS visit (and not completed in the most recent scheduled visit) will be required. The investigator may repeat any of the scheduled visit assessments as deemed clinically appropriate. These subjects will enter Study MLN0002-3029 for an observational LTFU period of 2 years after the last dose of study drug. During the LTFU period, data will be collected either by clinic visit or, if site attendance is not feasible, will be collected by phone call every 6 months.

Subjects who discontinue from the follow-up safety, but do not withdraw assent or whose legally authorized representative/adult caregiver does not withdraw consent, will complete assessment for a final follow-up safety visit as soon as possible. These subjects will enter Study MLN0002-3029 for an observational LTFU period of 2 years after the last dose of study drug. During the LTFU period, data will be collected either by clinic visit or, if site attendance is not feasible, will be collected by phone call every 6 months.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications 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 study material.

8.1 Study Drug 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 (ID) 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

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

Vedolizumab IV must be stored at 2ºC to 8ºC (36ºF-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

The dose and dosing regimen for subjects in this study are provided in Table 8.a.

During the induction period, subjects ≥30 kg will receive open-label vedolizumab, 300 mg IV at Day 1, Week 2, and Week 6; subjects who weigh >15 to <30 kg will receive an open-label dose of vedolizumab 200 mg IV at Day 1, Week 2, and Week 6; and subjects who weigh 10 to 15 kg will receive an open-label dose of vedolizumab 150 mg IV at Day 1, Week 2, and Week 6.

The infusion will be administered IV 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.

At Week 14, those who achieve a **clinical response** (as defined in Section 6.1) will be stratified by previous exposure/failure to TNF-α antagonists therapy or naïve to TNF-α antagonists therapy and weight (as determined at Week 14) and randomized 1:1 to one of 2 dose groups, within each weight group, for the double-blind maintenance period.

Table 8.a Dose and Regimen

Treatment Period	Weight	Vedolizumab IV Dose	Treatment Regimen
	Weight at Baseline		
Induction (open-label)	10 kg to 15 kg	150 mg	Day1, Week 2, Week 6
	>15 kg to <30 kg	200 mg	
	≥30 kg	300 mg	
	Weight at Week 14		
Maintenance (double-blind)	10 kg to 15 kg	150 mg	Q8W from Weeks 14 through 46
		100 mg	
	>15 kg to <30 kg	200 mg	
		100 mg	
	≥30 kg	300 mg	
		150 mg	

IV: intravenous; Q8W: once every 8 weeks.
Adjustments to the maintenance dose only as described for lack of maintenance of clinical response and worsening of disease; no adjustments made strictly on the basis of weight change over time.

8.1.4 Overdose

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

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

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

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

8.2 Study Drug Assignment and Dispensing Procedures

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

The investigator or investigator's designee will access the interactive web response technology (IRT) system at screening to obtain the subject study number. The investigator or the investigator's designee will use the IRT to enroll (Day 1) the subject in the open-label induction phase and to randomize the subject into the maintenance phase at the Week 14 visit. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. The medication ID number of the study 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 study drug for a subject, and the medication ID number of the study drug to be dispensed will be provided by the IRT.

8.3 Study Drug Blind Maintenance

The study drug blind will be maintained using the IRT.

8.4 Unblinding Procedure

The study drug blind may be broken by the investigator if information concerning the study 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 study drug blind can be obtained by the investigator, by accessing the IRT.

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

8.5 Accountability and Destruction of Sponsor-Supplied Drugs

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

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

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment in the IRT. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

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

- Frequently verifying that the 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.

In acknowledgement of hospital, local, state, or national government restrictions or other site-related factors caused by unavoidable circumstances (ie, COVID-19 pandemic), which 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). Investigators are expected to evaluate the impact on the safety of the study subjects and site personnel for subjects to continue. In evaluating such requests, the medical monitor will give the highest priority to the safety and welfare of the subjects. For subjects that are impacted, 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 study team (and the medical team as needed), while maintaining patient safety and confidentiality as priorities.

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

- Endoscopy visit windows for Weeks 14 and 54 may be extended to ±7 days to provide more flexible scheduling.
- Deviations from protocol-specified procedures (eg, not collecting a study sample such as postdose bloodwork) will be recorded as related to a pandemic (eg, COVID-19 or other similar pandemic).

9.1.1 Informed Consent Procedure

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

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

A unique subject ID number (subject number) will be assigned to each subject at the time of screening by the IRT; this subject number will be used throughout the study.

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

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information of the subject will be obtained at screening may include (depending on local regulations):

- Date of birth or age.
- Sex at birth.
- Ethnicity:
  – Hispanic or Latino.
  – Not Hispanic or Latino.
  – Not reported.
  – Unknown.
- Race as described by the subject (select all that apply):
  – American Indian or Alaska Native.
  – Asian.

  Asian Sub-Category:
    - Asian Indian.
    - Chinese.
    - Filipino.

- Japanese.
- Korean.
- Vietnamese.
- Not reported.

– Black or African American.

– Native Hawaiian/other Pacific Islander.

– White.

– Not reported.

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

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases including those relevant to the disease under study that stopped at or prior to signing of the subject's informed consent or parental informed consent form and/or pediatric assent form, as required by local regulations. Ongoing conditions are considered ongoing medical history.

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 1 month prior to signing of the subject's informed consent or parental informed consent form and/or pediatric assent form, as required by local regulations. Vaccination history does not need to be documented as medication history, and vaccination status will be recorded as part of the inclusion and exclusion criteria.

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

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) GI system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. Clinically significant findings will be recorded as medical history if the start date is before first dose of study drug (Day 1). All subsequent physical examinations should assess clinically significant changes from the assessment before the first-dose physical examination. Clinically significant findings will be recorded as AEs if they start after the first dose of study drug in this study. A Tanner Stage Evaluation (Section 9.1.19) will be performed at screening and at the EOS/final treatment visit.

9.1.4 Weight and 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 Sign Procedure

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

9.1.6 Primary Efficacy Measurement

Modified, complete, and/or partial Mayo scores (see Appendix I and Appendix L) will be calculated at screening and at scheduled visits during the study as per the Schedule of Study Procedures (Appendix A) using the subject's/parent's or legal guardian's daily diary entries. During screening, subjects/parents or legal guardians will be instructed on how to appropriately complete the diary. Subjects/parents or legal guardians will make daily entries into the diary to record the symptoms of UC throughout the study, including the screening period. Entries should be reviewed and monitored by the study staff. Diary entries preceding each study visit will be used to calculate the Mayo score.

High compliance is expected regarding e-diary recording from the subject/caregiver throughout the study. Compliance will be assessed by the site staff after 7 days of the start of e-diary recordings, and the subject/caregiver should be retrained on the appropriate use of the e-diary when compliance is below 80%. Noncompliant subjects with missing modified Mayo score due to insufficient e-diary entries could be automatically noneligible for enrollment in the induction and/or maintenance period.

A modified and complete Mayo score will be evaluated during screening by using subject diary entries and endoscopy results. The Physician's Global Assessment (PGA) form as part of the Mayo score should be completed on the first day of screening. When endoscopy is performed during screening, at least 7 days of diary entries should be collected before the endoscopy is performed. Because the endoscopy 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 endoscopy preparation is administered. If historic endoscopy is used, at least 7 days of diary entries should be collected after the PGA form is completed before the Mayo score can be generated. Please refer to Appendix I for appropriate reporting of stool frequency and rectal bleeding as part of the Mayo score calculation. 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 endoscopy preparation is administered. A modified Mayo score will be evaluated at Day 1 before the first

infusion. A modified and complete Mayo score will also be evaluated (before dosing) at Week 14 and at Week 54 (or ET visit if appropriate).

A partial Mayo score will be derived at Day 1, at scheduled visits during the study, and at any unscheduled visit(s) due to disease exacerbation as per the Schedule of Study Procedures (Appendix A).

The modified Mayo score excludes the Physician's Global Assessment (composed of the sum of stool frequency subscore, rectal bleeding subscore, and endoscopic subscore; this is modified so that a score of 1 does not include friability) and ranges from 0 to 9. The partial Mayo score excludes endoscopy (composed of the sum of stool frequency subscore, rectal bleeding subscore, and Physician's Global Assessment subscore) and ranges from 0 to 9.

The complete Mayo score includes endoscopy (composed of the sum of stool frequency subscore, rectal bleeding subscore, endoscopic subscore [this is modified so that a score of 1 does not include friability], and Physician's Global Assessment subscore) and ranges from 0 to 12.

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject or subject's legally authorized representative/adult caregiver. Concomitant medication is not provided by Takeda. A concomitant procedure is any nonpharmacological medical intervention used to treat a subject's UC.

At each study visit (from signing of subject/parental informed consent and/or subject assent, as required by local regulations, through the end of the study), subjects or subject's legally authorized representative/adult caregivers will be asked whether they have taken any medication other than the study drug or undergone any procedures to treat their UC. All medication (including vitamin supplements, OTC medications, and oral herbal preparations) and concomitant procedures must be recorded in the eCRF.

9.1.8 Documentation of Concurrent Medical Conditions

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

9.1.9 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood collected at any single visit (including blood collection for PK analysis) is approximately 12 mL for subjects weighing ≥30 kg and 7.9 mL for subjects weighing 10 to <30 kg. The approximate total volume of blood for the study is 100 mL for subjects ≥30 kg and 65.1 mL for subjects weighing 10 to <30 kg.

Details of these procedures and required safety monitoring will be provided in the laboratory manual. Clinical laboratory tests to be conducted are summarized in Table 9.a.

The central laboratory will perform all laboratory tests with the exception of the following: (1) urine pregnancy tests, which will be performed at the study site; and (2) fecal calprotectin, screening or unscheduled visit stool tests may be performed at the local laboratory at the investigator's discretion. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

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

NOTE: All requests for rescreening/retesting should be referred to the medical monitor.

Additional information and instructions can be found in the laboratory manual.

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, 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 LFTs in relation to ALT or AST >3× ULN in conjunction with total bilirubin >2× ULN.)

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

Table 9.a Clinical Laboratory Tests

Hematology	Clinical chemistry
RBC	ALT
WBC with differential	Albumin
Hemoglobin	Alkaline phosphatase
Hematocrit	AST
Platelets	Direct bilirubin
INR (if required)	Total bilirubin
	Total protein
	Creatinine
	Blood urea nitrogen
	Creatine kinase
	GGT
	Potassium
	Sodium
	Glucose
	Chloride
	Bicarbonate
	Calcium
	Amylase

Table 9.a Clinical Laboratory Tests

Hematology	**Clinical chemistry**
	CRP
Other:	
Serum	**Urine**
HIV test Hepatitis panel, including HBsAg, HBcAb, HBsAb, and anti-HCV QuantiFERON test [a] AVA Female subjects only: beta hCG [b] Female subjects only who are menstruating (regardless of age) or aged ≥11 years [b]	Female subjects only: hCG (urine pregnancy test) (Female subjects only who are menstruating or aged ≥11 years, whichever is younger) [b]
Stool [c]	
Clostridioides difficile testing and toxin A and B Fecal calprotectin Ova and parasite evaluation Stool culture	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; AVA: antivedolizumab antibodies; CRP: C-reactive protein; ET: early termination; GGT: γ-glutamyl transferase; hCG: human chorionic gonadotropin; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; INR: international normalized ratio; RBC: red blood cell; TB: tuberculosis; WBC: white blood cell.

[a] TB skin test can be performed as alternative for screening.

[b] Serum pregnancy analysis is performed at the screening, Week 54/ET, and follow-up safety visits. Urine pregnancy analysis is performed at all other scheduled visits as specified in Appendix A.

[c] With the exception of fecal calprotectin, screening or unscheduled visit stool tests may be performed locally at the investigator's discretion.

9.1.10 Contraception and Pregnancy Avoidance Procedure

9.1.10.1 Male Subjects and Their Female Partners

From signing of subject informed consent or parental informed consent and/or subject assent form, as required by local regulations, throughout the duration of the study, and for 18 weeks after last dose of study drug, male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective contraception (Section 9.1.10.3).

9.1.10.2 Female Subjects and Their Male Partners

From signing of subject informed consent or parental informed consent and/or subject assent form, as required by local regulations, throughout the duration of the study, and for 18 weeks after last dose of study drug, female subjects of childbearing potential* who are sexually active

with a nonsterilized male partner** must use a highly effective method of contraception (from the list below). In addition, they must be advised not to donate ova during this period. **This will apply to female subjects of childbearing potential who are menstruating (regardless of age) or are aged ≥11 years prior to or during the study.**

9.1.10.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A female subject is considered a female subject of childbearing potential, that is, fertile, following menarche unless permanently sterile. Permanent sterilization methods include hysterectomy and bilateral oophorectomy.

** 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 until she has been on contraceptive for 3 months:

– Oral.

– Injectable.

– Implantable.

2. Unacceptable methods of contraception in this study 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.
- Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
- Spermicides only.
- Withdrawal.
- No method at all.
- Use of female and male condoms together.
- Cap/diaphragm/sponge without spermicide and without condom.

3. Subjects will be provided with information on highly effective methods of contraception as part of the subject/parental informed consent and/or subject 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.

4. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for female subjects of childbearing potential (or who have reached menarche) 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:

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

– Is there a chance you could be pregnant?

5. Female subjects only who are menstruating or aged ≥11 years, whichever is younger, must have a negative serum pregnancy at screening and a negative urine pregnancy test before each infusion.

9.1.11 Pregnancy

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

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

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

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.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum and 1 year postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion, or congenital abnormality are considered SAEs and must be reported using the Takeda SAE eCRF or SAE form.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Takeda SAE eCRF or SAE form as well as the pregnancy form. The test date of the first positive serum/urine β hCG test or ultrasound result will determine the pregnancy onset date.

9.1.12 PK Sample Collection and Analysis

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

- Day 1 (1 sample obtained post dose).
- Weeks 2, 6, and 46 (2 samples obtained 1 sample predose and 1 sample post dose).
- Weeks 14, 22, 30, and 38 (1 sample obtained predose).
- Week 10, Week 54/EOS/ET, final safety visit, and any unscheduled visit (1 sample obtained any time during visit).

Predose PK samples should be obtained within 30 minutes before dosing. Postdose PK samples should be obtained within 60 minutes after the end of the infusion. Detailed instructions on collection and processing of PK samples are included in the laboratory manual.

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

The samples may be stored for up to 15 years in a biorepository.

9.1.13 Immunogenicity Sample Collection

Blood samples for the assessment of AVA will be collected as shown in the Schedule of Study Procedures (Appendix A). Samples will be obtained within 30 minutes prior to dosing, where applicable, at Day 1; Weeks 6, 14, 30, 46, and 54; and at any unscheduled visit for a subject who experiences an SAE or disease exacerbation. For subjects who do not continue treatment with vedolizumab in the extension study, the final assessment for AVA will be performed 18 weeks after the last dose of study drug. A sample will be assessed for neutralizing AVA if a positive AVA is detected.

Positive AVA samples will be tested for titers and neutralizing ability using previously validated assays. The exact sampling times must be recorded accurately for all immunogenicity samples.

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

The samples may be stored for up to 15 years in a biorepository.

9.1.14 TB Screening

All subjects will complete TB screening, using QuantiFERON or the tuberculin skin test, to determine eligibility. Subjects will be excluded from the study if they have active or latent TB.

NOTE: Subjects with documented previously treated TB with a negative QuantiFERON test can be included in the study, as defined in Section 7.2.

9.1.15 Fecal Calprotectin Sample Collection

Fecal calprotectin is a biomarker of intestinal inflammatory activity. A stool sample will be collected for analysis during screening, at home prior to the Week 14 and Week 54 visits (or ET visit if subject withdraws prior to Week 54), and at any unscheduled visits due to disease exacerbation. The stool sample must be collected before any bowel preparation that is given for endoscopy. This sample must be analyzed by the central laboratory.

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

A stool sample will be obtained for culture, ova and parasite evaluation, and *C difficile* assay. A sample will be collected and cultured during screening and at any point in the study when a subject becomes symptomatic, including worsening of UC. Screening or unscheduled visit stool tests may be performed locally at the discretion of the investigator.

9.1.17 PUCAI

PUCAI is an instrument for assessment of disease activity in children and adolescents with UC based on evaluation of 6 clinical measures (see Appendix J and Appendix L). A PUCAI score will be assigned by the investigator at screening and then at every scheduled visit during the study as per the Schedule of Study Procedures (Appendix A).

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

The IMPACT-III questionnaire is a self-reported measure with 35 closed questions encompassing 6 domains: Bowel Symptoms (7 items), Systemic Symptoms (3 items), Social Functioning (12 items), Body Image (3 items), Treatment/Interventions (3 items), and Emotional Functioning (7 items) (Appendix L). 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 will be administered to subjects aged 9 to 17 years at the time of first dose of study drug and at Weeks 14 and 54. Entries should be reviewed and monitored by the study staff.

The current version of the IMPACT-III questionnaire will be provided in the study manual.

9.1.19 Tanner Stage Evaluation

Tanner Stage Evaluation (see Appendix K) 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 as specified in the Schedule of Study Procedures (Appendix A).

9.1.20 Endoscopies

A colonoscopy will be performed during screening (unless one has already been performed as SOC within 30 days prior to signing of subject/parental informed consent and/or subject assent and the video recording is acceptable by central readers for baseline assessment), and a flexible sigmoidoscopy will be performed at Weeks 14 and 54 (or ET visit). When scheduling the

endoscopy, please allow sufficient time for centrally read results as well as assessment of laboratory and severity of symptoms. Because the endoscopy 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 endoscopy preparation is administered. Endoscopies will be read centrally for the efficacy analysis, for the screening endoscopy, and for the Week 14 and 54 visit endoscopies (or ET visit if appropriate), through use of video recordings. An ET endoscopy is not required if a subject withdraws before Week 6 during the induction phase or by Week 30 during the maintenance phase. On the days that endoscopies are performed, all other study procedures for that visit should be performed either prior to the endoscopy or on another day within the visit window.

9.1.21 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 reason for screen failure will be collected. The IRT should be contacted as a notification of screen failure.

The primary reasons for screen failure are as follows:

- AE.
- Screen failure (did not meet inclusion criteria or did meet exclusion criteria).
- Protocol deviation.
- Lost to follow-up.
- Withdrawal by subject.
- Withdrawal by parent/guardian.
- Study terminated by sponsor.
- Other.

Subject numbers assigned to subjects who fail screening should not be reused even if the subject is eligible to be rescreened. Subjects who are screen failures may be rescreened (up to 3 times) but need prior approval by the sponsor. The need for repeat screening labs and/or procedures should be discussed in advance of the rescreening with the sponsor.

9.1.22 Monitoring Subject Treatment Compliance

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

9.2 Schedule of Observations and Procedures

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

9.2.1 Screening

Subjects will be screened within 35 days before Day 1 (enrollment visit). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.21 for procedures for documenting screening failures.

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

9.2.2 Randomization and Stratification

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

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for the study, the subject should be randomized in the IRT, as described in Section 8.2. The randomization will be stratified by previous exposure/failure to TNF-α antagonists therapy or naive to TNF-α antagonists therapy, and by weight group (≥30 kg; >15 kg to <30 kg; 10 kg to 15 kg). Subjects will be given the first dose of study drug as described in Section 6.1. The procedure for documenting screening failures is provided in Section 9.1.21.

9.2.3 EOS or ET Visit

The EOS visit will be performed at Week 54 or at the ET visit. The procedures listed in Schedule of Study Procedures (Appendix A) at Week 54 will be performed and documented. The Week 54 visit is the end of study for subjects continuing to receive vedolizumab in the MLN0002-3029 extension study. If discontinuation occurs within 2 weeks after a scheduled visit, only assessments pertaining to the EOS visit (and not completed in the most recent scheduled visit) will be required. The investigator may repeat any of the scheduled visit assessments as seems clinically appropriate.

Subjects who do not qualify to continue receiving vedolizumab in the extension study or subjects who discontinue from the study treatment for any reason will complete the EOS/ET visit and the follow-up safety visit (18 weeks after last dose).

9.2.4 Final Safety Follow-up Visit

For subjects who ET or are not eligible to continue treatment with vedolizumab during the MLN0002-3029 extension study, a final on-study follow-up safety visit will be performed 18 weeks after the last dose of study drug. Assessments will be completed per the Schedule of Study Procedures (Appendix A).

9.2.5 Poststudy Care

Study drug will not be available upon completion of the subject's participation in the study except in countries where other drug access programs become available. The subject should be returned to the care of a physician and use standard therapies as required.

Subjects who maintain corticosteroid-free clinical response at Week 54 and are younger than 18 years will be eligible to continue to receive vedolizumab IV treatment in the MLN0002-3029 extension study. All other subjects will enter Study MLN0002-3029 for an observational LTFU period of 2 years after the last dose of study drug in the current study. During the LTFU period, data will be collected either by clinic visit or, if site attendance is not feasible, will be collected by phone call every 6 months.

9.2.6 Other Unscheduled Visits (if Applicable)

Subjects may return to the study center for unscheduled visits as needed. Unscheduled visits can be performed when the subject has a study-related issue in between regular visits (eg, SAE follow-up, LFT elevations). The following procedures may be done during these visits: concomitant medications, clinical laboratory blood draws, PK assessment, AVA assessment, urine sample, and AE collection, as appropriate. Endoscopy may be performed (only if deemed necessary per the investigator's discretion) AND complete/modified Mayo scores may be obtained (only if an endoscopy is performed). SOC visits (routine check-ups) should not be captured as an unscheduled visit in eCRF. However, if the visit is due to disease exacerbation, the procedures described in Section 9.2.7 should be performed.

9.2.7 Unscheduled Visits Due to Disease Exacerbation

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

- Physical examination (including height and weight).
- Vital signs assessment.
- Diary review.
- Collection of concomitant medications and procedures.
- Collection of AEs and SAEs.
- Clinical chemistry and hematology and CRP, as indicated.
- Stool sample for culture, ova and parasite evaluation, and *C difficile* assay.
- Stool sample for fecal calprotectin.
- Urine hCG for female subjects of childbearing potential.
- PUCAI.
- Partial Mayo score.
- AVA sample collection.
- PK assessment.

There is no minimum time for repeat evaluation by unscheduled visit to determine if a subject meets the criteria for lack of maintenance of clinical response and disease worsening

(Section 3.5). In general, however, enough time should be provided for clinically meaningful change to occur (eg, 1 week).

10.0 PTE AND AE

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
Nonserious adverse drug reactions related to AxMP	• Complete AE eCRF (If EDC is down, submit paper SAE form).	7 days

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

10.1 Definitions

10.1.1 PTEs

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

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.

- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

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

Pre-existing conditions:

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

to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

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

Changes in intensity of AEs/Serious PTEs:

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

Preplanned procedures (surgeries or interventions):

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

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

10.1.4 SAEs

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

1. Results in DEATH.

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

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

10.1.5 AESIs

An AESI (serious or nonserious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate (Section 10.2.1.3). Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

10.1.6 Intensity of PTEs and AEs

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

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

10.1.7 Causality of AEs

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

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

10.1.8 Relationship to Study Procedures

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

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

10.1.9 Start Date

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

10.1.10 Stop Date

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

10.1.11 Frequency

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

10.1.12 Action Concerning Study Drug

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

10.1.13 Outcome

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

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

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

Collection of AEs will commence from the time the subject is first administered study drug. Routine collection of AEs will continue until the final follow-up safety visit approximately 18 weeks after the last dose of the study drug for subjects who do not continue to receive treatment with vedolizumab in the MLN0002-3029 extension study.

For subjects who do continue to receive treatment with vedolizumab in Study MLN0002-3029, AEs will be collected in Study MLN0002-3024 until the first dose is administered in the extension study.

10.2.1.2 PTE and AE Reporting

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

Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Nonserious PTEs, related or unrelated to the study procedure, need not to be followed up for the purposes of the protocol.

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

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

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

10.2.1.3 AESIs

Infusion-Related Reactions and Hypersensitivity

Currently, there is no evidence to support the routine prophylactic administration of premedication (eg, antihistamines, corticosteroids) to subjects receiving vedolizumab; hence, such premedications are unlikely to be necessary or beneficial. At the discretion of the investigator, however, subjects may be administered premedication prior to any study drug administration. Corticosteroids, if given as a premedication, should be limited to the day of administration. Vedolizumab should be administered by a health care professional prepared to manage hypersensitivity reactions, including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use. Subjects should be

observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion.

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

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

Serious Infection

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

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

Infections that meet seriousness criteria will be reported as AESIs.

Malignancy

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

Other

Other AESIs include liver injury and PML. Liver injury is described further in Section 10.2.3.

PML

There have been confirmed cases of PML in immuno-compromised adult patients who received vedolizumab: (1) an HIV patient with CD and (2) an acute myeloid leukemia patient with acute graft-versus-host disease. Both patients had received prolonged or heavy immunosuppressive therapy and developed PML subsequently. The IAC concluded that the development of PML was probably related to the underlying diseases. Additional details are provided in the current edition of the investigator's brochure.

Subjects should be monitored for the development of any new onset or worsening of neurological signs and symptoms and consider neurological referral if they occur. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months.

If PML is suspected, the next dose of study drug will be held until the evaluation is complete and results are available. The subject should be urgently referred to a neurologist. Subsequent doses of study drug will be administered only if the possibility of PML is definitively excluded. If the neurologist rules out PML, dosing may resume. However, if the neurologist confirms PML or is unable to rule out PML, continue to withhold dosing with vedolizumab and contact the local medical monitor urgently. All such cases will be referred to the PML IAC for further evaluation. Treatment will be resumed only in cases where PML is ruled out by the IAC. The drug will be permanently withheld in cases where PML was confirmed or could not be ruled out by the IAC.

Educational materials to minimize the risk of PML will be distributed to all sites and are included in the study manual. Subjects will receive educational materials prior to receiving treatment. The informed consent form will contain specific information on the hypothetical risk of PML. Any documented case of PML will be reported as an SAE, regardless of whether hospitalization occurs.

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

10.2.2 Collection and Reporting of SAEs

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

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

- A short description of the event and the reason why the event is categorized as serious.
- Subject ID number.
- Investigator's name.

- Name of the study drug(s).
- Causality assessment.

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

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

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

10.2.3 Reporting of Abnormal Liver Associated Tests

If a subject is noted to have ALT or AST elevated >3× ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, for any 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 9.1.9 must also be performed.

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 AE Reporting for AxMPs

The causality for all AEs should be assessed against the AxMPs. Any SAEs deemed related to all AxMPs will follow the SAE reporting procedures described in Section 10.2.2.
All nonserious AEs assessed as related to the authorized AxMPs only should be reported to the sponsor within 7 days via methods described in Section 10.2.1.

10.3.2 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.

10.3.3 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 reports within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to its IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) has been established to review safety, PK, and other relevant data and to monitor the general safety of subjects who participate in the study. The DSMB may make recommendations on whether the study should be suspended or terminated based on the review of the data.

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

The composition of and working procedures for the DSMB are defined in the DSMB charter and will be provided to the DSMB members.

11.2 Adjudication Committee

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

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent or subject/parental informed consent and/or subject assent, as required by local regulations. Data from the eCRFs will also include data from the safety follow-up visit.

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 performance of this study to the sponsor and regulatory authorities. All eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the ID log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated assent/informed consent/assent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor, or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International 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 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

A statistical analysis plan (SAP) will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

If not otherwise mentioned, continuous variables will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum) and categorical variables will be summarized by frequency tables showing the number and proportion of subjects falling into each category.

13.1.1 Analysis Sets

The populations used for analysis will include the following:

- Intent-to-treat (ITT): The ITT analysis set will include all enrolled subjects for the induction phase; the ITT analysis will include all randomized subjects in the maintenance phase.

  ITT-M will include all subjects randomized in the maintenance phase.

  Subjects in these analysis sets are not required to receive any dose of vedolizumab to be included. In the induction phase, a subject is considered enrolled if the subject is eligible to enter the study and the informed consent form is obtained. In the maintenance phase, all subjects eligible to be randomized will be included in this analysis set. Subjects will be analyzed according to the treatment they were intended (induction phase) or randomized (maintenance phase) to receive, regardless of any errors of dosing.

The ITT will be used for efficacy analysis with exception of corticosteroid-free remission, which will be based on a subset of the ITT subjects with baseline concomitant oral corticosteroid use.

- Modified intent-to-treat (mITT): The mITT will include all randomized subjects who receive at least 1 dose of study drug. Subjects who only receive induction therapy and not randomized into the maintenance phase will not be included in the mITT. Subjects in this set will be analyzed according to the treatment they were randomized to receive.
- Per-protocol set (PPS): The PPS is a subset of the ITT. The PPS consists of all subjects who do not violate the terms of the protocol in a way that would impact the study outcome significantly. All decisions to exclude subjects from ITT for the PPS will be specified in the SAP prior to the unblinding of the study. Analyses of primary and secondary efficacy endpoints will be performed using the PPS as a sensitivity analysis, if more than 5% of the total subjects in the ITT are excluded from the PPS.
- Safety analysis set (SAF): The SAF will include all subjects who receive at least 1 dose of study drug. Subjects in this set will be analyzed according to the treatment that was actually received. SAF-I will include all subjects who receive at least 1 induction dose but were not randomized to maintenance phase. The SAF-M will include all subjects who receive at least 1 maintenance dose.
- PK analysis set: The PK evaluable population is defined as all subjects who receive at least 1 dose of vedolizumab and have measurable drug concentration in blood to allow for PK evaluation. PK-I is all subjects who receive at least 1 induction dose with measurable drug concentration in blood to allow for PK evaluation but were not randomized into the maintenance phase.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Baseline and demographic information for both induction and maintenance phases will be listed and summarized by treatment group and for the ITT population.

Medical history and concurrent medical conditions will be summarized by System Organ Class and Preferred Term. Medication history and concomitant medications will be summarized by therapeutic class and preferred term.

13.1.3 Efficacy Analysis

The PK exposure and response from each planned dose (ie, high dose, low dose) are expected to be similar across the 3 weight categories (≥30 kg; >15 to <30 kg; 10 to 15 kg). In other words, the high dose in the ≥30 kg weight group is expected to have similar effect as the high dose in the >15 to <30 kg and 10 to 15 kg weight groups. Similarly, the low doses within each weight category (≥30 kg; >15 to <30 kg; 10 to 15 kg) are expected to have similar effect. Therefore, the data across the 3 weight categories (≥30 kg; >15 to <30 kg; 10 to 15 kg) within each dose category (high dose, low dose) will be combined and analyzed by dose (high dose, low dose),

unless otherwise specified. The primary statistical objective in the efficacy analyses is the estimation of endpoints of interest. No formal hypothesis testing will be performed.

For binary endpoints, any subject with missing information for determination of endpoint status will be considered as a nonremitter/nonresponder at the respective timepoint. Subjects who had to switch to a higher dose due to lack of maintenance of clinical response and disease worsening or received rescue corticosteroids will be also considered nonremitters/nonresponders. All efficacy analyses will be performed on the ITT population, unless otherwise specified.

Primary Efficacy Endpoints

For the primary endpoint, clinical remission at Week 54, the point estimate of the clinical remission rate, and the associated 95% Pearson-Clopper CIs will be presented by dose groups (high dose, low dose).

Secondary Efficacy Endpoints

The proportion-based secondary efficacy endpoints are:

- Clinical remission at Week 14.
- Sustained clinical remission at Weeks 14 and 54.
- Sustained endoscopic remission at Weeks 14 and 54.
- Endoscopic response at Week 14.
- Endoscopic response at Week 54.
- Corticosteroid-free clinical remission at Week 54.
- Clinical remission based on complete Mayo score at Week 54.
- Clinical response at Weeks 2, 6, 10, 14, 22, 30, 38, 46, and 54.
- Clinical remission at Weeks 2, 6, 10, 14, 22, 30, 38, 46, and 54.
- Sustained clinical response of subjects at Weeks 14 and 54.

All proportion-based secondary efficacy endpoints will be analyzed similarly as done for the primary endpoint.

Comparisons of clinical remission and clinical response rates between pediatric and adult populations will be performed and reported separately on primary and key secondary endpoints as follows:

- Populations: An adult population will be selected from completed studies of vedolizumab IV in adults with UC (vedolizumab IV and placebo arms) to be similar to the pediatric population in Study MLN0002-3024. Differences in the adult and pediatric study designs will be taken into account, including the duration of the induction period and the criteria required to proceed to maintenance period.

- Endpoints: Primary and secondary endpoints at Week 14 and Week 54, including clinical response and clinical remission at Week 14 (end of induction period), clinical remission at Week 54 (end of maintenance period), sustained remission at Week 54, and corticosteroid-free remission at Week 54.
- Analysis and data presentation: Point estimates and 95% CIs will be provided for all treatment groups—pediatric subjects assigned to the vedolizumab IV high dose, pediatric subjects assigned to the vedolizumab IV low dose, adult subjects assigned to the vedolizumab IV arm, and adult subjects assigned to the placebo arm. Moreover, Bayesian methods utilizing adult data in the analysis of pediatric study will be explored.

Comprehensive details on the population selection and analysis methods will be provided in a separate SAP.

A systematic review and meta-analysis of randomized controlled studies of adult subjects with UC will be conducted to examine the pooled estimate of the Week 54 clinical remission rate for placebo arms. Such meta-analysis will be prespecified to address the differences in characteristics between pediatric and adult studies.

The continuous based secondary endpoint are:

- Change from baseline in weight gain and linear growth z-score during the course of dosing with vedolizumab.

For continuous endpoints, descriptive statistics (nonmissing values, mean, median, standard deviation, minimum, and maximum) and corresponding 95% CIs if applicable will be summarized by dose groups (high dose, low dose).

Shift analysis of Tanner stage will be performed at Week 54 compared with baseline, each domain separately.

Immunogenicity

The subjects' overall AVA status (negative, positive) and proportion of subjects with any positive neutralizing AVA during the study will be summarized.

- A negative AVA subject is defined as a subject who has negative AVA results at all time points during the study, from baseline/predose to the subject's last assessment (including the final safety visit).
- A positive AVA subject is defined as a subject who has at least 1 confirmed positive AVA result during the study, from baseline/predose to the subject's last assessment (including the final safety visit) and is further categorized as:
  - Transiently positive: Defined as subject with at least 1 confirmed positive AVA sample and no consecutive positive AVA samples.
    - Baseline positive only: Defined as subjects with 1 confirmed positive AVA sample at baseline/predose and negative samples at all postdose* visits.

  - Persistently positive: Defined as subject with confirmed positive AVA samples at 2 or more consecutive visits.

- Any neutralizing AVA (nAVA) positive subject: Subject with any positive neutralizing AVA results during the study from baseline/predose to the subject's last assessment (including the final safety visit).

*Postdose refers to post 1st dose of study drug received in the study including final safety visit.

Furthermore, the AVA status (negative, positive) by study visit will be summarized. The confirmed positive samples will be reported in 5-fold serial dilution factors (10, 50, 250, 1250, 6250, 31250, etc) and by AVA titer category, defined as low (less or equal to 50), moderate (250 to 1250) and high (greater or equal to 6250).

The impact of immunogenicity on PK, efficacy, and safety (including injection site reactions and infusion-related reactions) will be explored.

Additional details will be included in the SAP as necessary.

13.1.4 PK Analysis

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

Exposure-response analysis in pediatric subjects will be performed as appropriate. Further details will be provided in the SAP.

Further analysis will be performed as deemed necessary and will not be reported in the clinical study report (CSR). Analysis details and results will be part of a separate standalone report.

13.1.5 Exploratory Analyses

Change from baseline in CRP, albumin, and fecal calprotectin by visit will be summarized descriptively over time by dose group.

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

Change from baseline in Mayo and PUCAI scores and subscores by visit will be summarized descriptively by visit by dose group. Clinical remission and clinical response based on PUCAI score, as binary endpoints, will be analyzed similar to the primary and secondary binary endpoints.

13.1.6 Safety Analysis

The safety analysis will be performed using the SAF. No statistical inference will be made for safety analysis.

Safety evaluations will be based on incidence, severity, and type of AEs and clinically significant changes or abnormalities in the patient's physical or neurological examinations, vital signs, ECG, and laboratory results. Descriptive statistics will be calculated.

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). TEAEs will be tabulated by primary System Organ Class, High Level Term (HLT), and Preferred Term. MedDRA will be used for coding AEs. To summarize the number of subjects with AEs, subjects reporting the same event more than once will have that event counted only once within each System Organ Class, HLT, and Preferred Term. Events that are considered related to treatment will also be tabulated. AEs will also be summarized by intensity. Deaths, subjects with SAEs, and events resulting in study discontinuation, if present, will be presented in separate data listings.

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

All safety data collected up to final database lock will be summarized. If additional safety data from follow-up visits are collected after final database lock, additional summary data and listings will be provided as a CSR addendum.

13.1.7 Missing Data Analysis

Missing data for dichotomous (ie, proportion-based) endpoints will be handled using the nonresponder imputation method, ie, any subject with missing information for determination of endpoint status will be considered as a nonresponder/nonremitter in the analysis.

Missing data for continuous endpoints will be imputed using last available postbaseline observation carried forward method. For subjects without any nonmissing postbaseline measurement, the missing data will be imputed using baseline observation carried forward method. Other missing data imputation method may be explored.

Additional details will be provided in the SAP, as applicable.

13.2 IA and Criteria for ET

An IA may be conducted when at least 90 subjects in the ≥30 kg cohort have completed the study through Week 54 or prematurely discontinued. The purpose of this IA would be to evaluate safety, efficacy, and PK of vedolizumab treatment through Week 54. This IA may support regulatory interactions and would be performed by an unblinded team not directly involved in study activities. A separate (blinded) study team would continue to support the ongoing study activities.

A subsequent IA (Week 54 IA) may be conducted when all enrolled subjects have completed the study through Week 54 or prematurely discontinued. In this IA, all efficacy and all safety data collected up to the Week 54 IA data cut would be summarized. Any additional data collected

after the Week 54 IA data cut will be included in the final analysis of the study. The Week 54 IA may support further regulatory interactions and/or submissions. At the time of the database lock for the Week 54 IA, all efficacy data would have been collected, and only a few subjects may be in the 18-weeks safety follow up period. Therefore, the Sponsor study team would be unblinded upon database lock of this interim data cut. However, the study subjects, their legal representatives and study physicians will be kept blinded until the last subject has completed the last study visit.

The final analysis of the study will be conducted when all subjects completed their last study visit. Additional details for the IAs will be provided in the SAP.

13.3 Determination of Sample Size

The primary statistical objective is the estimation of the primary endpoint, clinical remission at Week 54, by dose group (high dose, low dose). No formal hypothesis testing is planned. The sample size justification was based on ensuring adequate precision (using the half-width of the 95% CI) for the estimate of the true clinical remission rate.

Assuming the true clinical remission rate of 42% at Week 54, a sample size of 36 subjects in each maintenance arm will provide a 95% Clopper-Pearson exact CI with a lower bound of 25.5% and an upper bound of 59.2%. In addition, the table below summarizes the Clopper-Pearson exact 95% CI for the clinical remission rates ranging from 37% to 47% with a sample size of 36 subjects.

Observed Clinical Remission Rates With Clopper-Pearson 95% CI (for N = 36 subjects)	
Observed Remission Rate	**95% Clopper-Pearson CI**
37%	(20.8%-53.8%)
42%	(25.5%-59.2%)
47%	(27.9%-61.9%)

The width of this CI provides adequate precision around the primary endpoint of interest.

To ensure a randomized sample size of 72 subjects (36 per maintenance arm) during the maintenance phase, approximately 120 subjects will need to be enrolled in the induction phase of the 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. Monitoring may be done remotely where allowed by local regulations and ethics approvals. Source documents will be reviewed for verification of data recorded in the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

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

14.2 Protocol Deviations

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

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, 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 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 Guidelines 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 C. 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/parental informed consent and/or subject assent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification from the sponsor or designee, no protocol activities, including screening, may occur.

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

The assent/informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the assent/informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally authorized representative may provide such consent 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 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 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 form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

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

subject's medical record. Copies of the signed assent/informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised assent/informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally authorized representative in the same manner as the original assent/informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised assent/informed consent 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 trial database or documentation via a subject ID 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 ID 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 the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

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

15.4.2 Clinical Trial Registration

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

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

Any investigator who objects to 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 and/or other publicly accessible websites, as required by Takeda Policy/Standard and applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study

subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

	Screening	Induction Period				Maintenance Period						Follow-up Safety Visit [a]	Unscheduled Visit [b]
	Days -35 to -1	Day 1	Wk 2	Wk 6	Wk 10	Wk 14	Wk 22	Wk 30	Wk 38	Wk 46	Wk 54/ EOS/ET Visit [a]		
	NA	NA	±2 days	±2 days	±3 days	±7 days	±3 days	±3 days	±3 days	±3 days	±7 days	±1 week	
Assessment	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**NA**	
Subject/parental informed consent and/or subject assent [c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Allergy reaction card	X												
Patient alert card	X												
Demographics	X												
Medical history	X												
Medication history	X												
Tanner staging	X										X		
Physical examination [d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight and height [e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs [e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
IRT accessed	X	X	X	X		X	X	X	X	X	X		
PTE assessment [f]	X	X											
AE assessment [g]		X	X	X	X	X	X	X	X	X	X	X	X
Endoscopy [h]	X					X					X		X
Dosing		X	X	X		X	X	X	X	X			
Clinical Outcomes Assessments													
PUCAI	X	X	X	X	X	X	X	X	X	X	X		X
Complete Mayo	X					X					X		X
Modified Mayo	X	X				X					X		X
Partial Mayo		X	X	X	X	X	X	X	X	X	X		X

	Screening	Induction Period				Maintenance Period						Follow-up Safety Visit [a]	Unscheduled Visit [b]
	Days -35 to -1	Day 1	Wk 2	Wk 6	Wk 10	Wk 14	Wk 22	Wk 30	Wk 38	Wk 46	Wk 54/ EOS/ET Visit [a]		
	NA	NA	±2 days	±2 days	±3 days	±7 days	±3 days	±3 days	±3 days	±3 days	±7 days	±1 week	
Assessment	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**NA**	
Electronic diary [i]	X	X	X	X	X	X	X	X	X	X	X		X
IMPACT-III		X				X					X		
Laboratory assessments													
TB screening [j]	X												
Serum pregnancy test [k]	X										X	X	
Urine pregnancy test [k]		X	X	X	X	X	X	X	X	X			X
HBV, HCV, HIV	X												
Stool samples (culture, O&P, *C diff*) [l]	X												X
Stool sample for fecal calprotectin [m]	X					X					X		X
Clinical chemistry (incl CRP)	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X
PK assessment [n]		X	X	X	X	X	X	X	X	X	X	X	X
AVA assessment [o]		X		X		X		X		X	X	X	X

AE: adverse event; AVA: antivedolizumab antibody; CD: Crohn's disease; *C diff*: *Clostridioides difficile*; CRP: C-reactive protein; EOS: end-of-study; ET: early termination; HBV: hepatitis B virus; HCV: hepatitis C virus; incl: including; IRT: interactive response technology; NA: not applicable; O&P: ova and parasite; PK: pharmacokinetic; PTE: pretreatment event; PUCAI: Pediatric Ulcerative Colitis Activity Index; SAE: serious adverse event; TB: tuberculosis; UC: ulcerative colitis; Wk: week.

[a] EOS/ET and follow-up safety visits: After the Week 54 EOS/ET visit assessments have been completed, subjects may be eligible to receive continued treatment with vedolizumab in extension Study MLN0002-3029. Subjects who do **not** qualify to receive continued treatment in the extension study or subjects who discontinue from the study for any reason will complete the EOS/ET visit and the follow-up safety visit (18 weeks after last dose). These subjects will then enter Study MLN0002-3029 for an observational LTFU period of 2 years after the last dose of study drug. In case of ET at the time of a scheduled visit, any assessments for ET already performed as part of the scheduled visit will not be repeated. If discontinuation occurs within 2 weeks after a scheduled visit; only assessments pertaining to the EOS visit (and not completed in the most recent scheduled visit) will be required. The investigator may repeat any of the scheduled visit assessments as deemed clinically appropriate.

[b] Subjects seen at an unscheduled visit for disease exacerbation will complete the unscheduled visit assessments per Section 9.2.7. Other unscheduled visits may include concomitant medications, vital signs, clinical laboratory blood draws, PK assessment, AVA assessment, urine sample, and AE collection as appropriate. IRT may include an unscheduled visit to allow for sites to make dose modifications between scheduled visits or to place a subject on dose hold. Endoscopy may be performed (only if deemed necessary per the investigator's discretion) AND complete/modified Mayo scores may be obtained (only if an endoscopy is performed).

[c] Subject age will be assessed at each study visit to confirm that their current informed consent and/or subject assent is applicable. If informed consent and/or subject assent needs to be updated because of age change, this will be done before any study procedures.

[d] Physical examination: Clinically significant findings will be recorded as AEs if they start after the first dose of study drug.

	Screening	Induction Period				Maintenance Period						Follow-up Safety Visit [a]	Unscheduled Visit [b]
	Days -35 to -1	Day 1	Wk 2	Wk 6	Wk 10	Wk 14	Wk 22	Wk 30	Wk 38	Wk 46	Wk 54/ EOS/ET Visit [a]		
	NA	NA	±2 days	±2 days	±3 days	±7 days	±3 days	±3 days	±3 days	±3 days	±7 days	±1 week	
Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	NA	

[e] Weight, height, and vital signs will be measured on clinic dosing days before dosing.
[f] PTEs will be captured immediately following the signing of the informed consent/pediatric assent at screening and until the first dose of study drug.
[g] Collection of AEs, to include concomitant medications, and SAEs will begin following the first dose of study drug and will be done before each dose on dosing days through the Week 54/EOS/ET visit and follow-up safety visit, if applicable, and at any unscheduled visit.
[h] Colonoscopy will be performed at screening within 30 days of signing informed consent/pediatric assent. Video endoscopy (flexible sigmoidoscopy) to be performed at Week 14 and Week 54, or EOS/ET if subject discontinues study drug early during the maintenance phase (after Week 30). When scheduling the endoscopy, allow sufficient time for centrally read results as well as assessment of laboratory results and severity of symptoms. Because the endoscopy 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 endoscopy preparation is administered.
[i] Electronic diary training will be provided to subjects/parents/legal guardians at screening. Diary entries are to be completed daily for all subjects. An average of 3 days of completed diary data before the Day 1 visit will be required for Mayo score calculation. Diary entries preceding each subsequent study visit (7 days) will be used to calculate the Mayo score. Because the endoscopy 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 endoscopy preparation is administered.
[j] TB screening may be completed using QuantiFERON or the tuberculin skin test.
[k] All female subjects who are menstruating or aged ≥11 years, whichever is younger, must have a serum pregnancy test at screening and at the Week 54/EOS/ET visit and the follow-up safety visit. A urine pregnancy test will be completed before each dose of study drug. Urine pregnancy tests may be performed locally.
[l] A stool sample will be obtained for culture, ova and parasite evaluation, and *C difficile* assay. A sample will be collected and cultured during screening and at any point in the study when a subject becomes symptomatic, including worsening of UC. Stool tests may be performed locally at discretion of the investigator.
[m] Fecal calprotectin stool sample must be collected before any bowel preparation that is given for endoscopy. These samples must be analyzed by the central laboratory.
[n] Day 1: 1 sample (obtained postdose); Weeks 2, 6, and 46: 2 samples (predose and postdose); Weeks 14, 22, 30, and 38: 1 sample (predose); Week 10, Week 54/EOS/ET, final safety visit, and any unscheduled visit: 1 sample (any time during visit). Predose PK samples will be obtained within 30 minutes before dosing. Postdose PK samples will be obtained within 60 minutes after the end of the infusion.
[o] All AVA samples will be obtained predose (within 30 minutes before dosing) if collected on dosing days.

Appendix B AxMPs

Product Class	Corticosteroids	Corticosteroids
Designation	AxMP (rescue medicine)	AxMP (rescue medicine)
Identification in the Protocol	Corticosteroids (prednisone or its equivalent)	Corticosteroids (prednisone or its equivalent)
Marketing Authorization	Yes	Yes
Used Within Marketing Authorization	Yes	Yes
ATC Code	A07EA	H02AB
Dose Formulation	Per discretion of investigator	Per discretion of investigator
Dose Strength(s)	Per discretion of investigator	Per discretion of investigator
Route of Administration	PO	PO
Dose Regimen	Dosing may not exceed 40 mg per day or 1 mg/kg/day (whichever is lower).	Dosing may not exceed 40 mg per day or 1 mg/kg/day (whichever is lower).
Duration	Taper per protocol (Section 7.3.1.1.2)	Taper per protocol (Section 7.3.1.1.2)
Arm (participants receiving the medicinal product)	A one-time rescue with corticosteroids is possible during the maintenance period of this study.	A one-time rescue with corticosteroids is possible during the maintenance period of this study.
Sourcing	Provided locally by the study site at the discretion of the investigator.	Provided locally by the study site at the discretion of the investigator.

ATC: Anatomical Therapeutic Chemical; AxMP: auxiliary medicinal product; PO: oral.

Appendix C 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 (by signing a Form FDA 1572):

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 that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB 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 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. 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 D 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 case report forms 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 E Elements of the Subject Informed Consent

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

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally 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 otherwise is entitled, and that the subject or the

subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

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

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from screening throughout the duration of the study and for 5 half-lives after last dose. 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 the study, study drug will be discontinued, and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 5 half-lives after last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix F 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 G Approximate Blood Volume (mL)

	Subjects 10 to <30 kg												
Sample Type	**SCR**	**Day 1**	**Wk 2**	**Wk 6**	**Wk 10**	**Wk 14**	**Wk 22**	**Wk 30**	**Wk 38**	**Wk 46**	**Wk 54/ EOS/ET Visit**	**Follow-up Safety Visit**	**Total Volume (mL)**
AVA		3.5		3.5		3.5		3.5		3.5	3.5	3.5	24.5
Chemistry (including CRP) [a]	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	13.2
Hematology	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	7.2
PK		1	2	2	1	1	1	1	1	2	1	1	14
Serology (HBV, HCV, HIV)	2.2												2.2
TB [b]	4												4
Totals	**7.9**	**6.2**	**3.7**	**7.2**	**2.7**	**6.2**	**2.7**	**6.2**	**2.7**	**7.2**	**6.2**	**6.2**	**65.1**

	Subjects ≥30 kg												
Sample Type	**SCR**	**Day 1**	**Wk 2**	**Wk 6**	**Wk 10**	**Wk 14**	**Wk 22**	**Wk 30**	**Wk 38**	**Wk 46**	**Wk 54/ EOS/ET Visit**	**Follow-up Safety Visit**	**Total Volume (mL)**
AVA		3.5		3.5		3.5		3.5		3.5	3.5	3.5	24.5
Chemistry (including CRP) [c]	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	30
Hematology	2	2	2	2	2	2	2	2	2	2	2	2	24
PK		1	2	2	1	1	1	1	1	2	1	1	14
Serology (HBV, HCV, HIV)	3.5												3.5
TB [b]	4												4
Totals	**12**	**9**	**6.5**	**10**	**5.5**	**9**	**5.5**	**9**	**5.5**	**10**	**9**	**9**	**100**

AVA: antivedolizumab antibodies; CRP: C-reactive protein; EOS: end-of-study; ET: early termination; HBV: hepatitis B virus; HCV: hepatitis C virus; PK: pharmacokinetics; SCR: screening; TB: tuberculosis; Wk: week.

[a] An additional 1.1 mL will be drawn for a serum pregnancy test in female subjects only who are menstruating or aged ≥11 years, whichever is younger, at the screening, Week 54/ET, and follow-up safety visits.

[b] A TB skin test for screening can be performed as an alternative to the QuantiFERON test.

[c] A serum pregnancy test will be performed in female subjects only who are menstruating (regardless of age) or aged ≥11 years at the screening, Week 54/ET, and follow-up safety visits.

These are estimated blood volumes. Please refer to the central and local laboratory-provided documents for the specific blood volumes collected by these laboratories.

Appendix H Procedure and Specimen Collections Unique to This Protocol

Specimen or Procedure	Performed? (Yes/ No)	Endpoint	When
Banked	No		
Fresh	No		
Immunogenicity			
Serum	Yes	AVA analysis	Day 1, Weeks 6, 14, 30, 46, 54, follow-up safety visit, and unscheduled visit, if needed
Pharmacokinetics			
Serum	Yes	Specimens for PK analysis	Day 1, Weeks 2, 6, 10, 14, 22, 30, 38, 46, 54, follow-up safety visit, and unscheduled visit, if needed
Plasma	No		
Urine	No		
Genotyping			
Blood	No		
Pharmacodynamics (includes biomarkers and ECGs for QTc measurement)			
Serum	No		
Plasma	No		
Urine	No		
ECGs	No		
Holter	No		
Other	Yes	Fecal calprotectin	Screening, Weeks 14 and 54
Special Imaging			
Tumor imaging (eg, PET scans)	No		
Organ function (eg, MUGA scans)	No		

AVA: antivedolizumab antibody; ECGs: electrocardiograms; MUGA: multigated acquisition scan; PET: positron emission tomography; PK: pharmacokinetics; QTc: QT interval corrected for heart rate.

Appendix I Scoring System for the Assessment of Ulcerative Colitis Activity

CCI

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 (Schroeder et al. 1987).

CCI

Appendix J PUCAI

CCI

[redacted]

Adapted from: Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology*. 2007;133(2):423-32 (Turner et al. 2007).

Appendix K 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 increase after 16 years.

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

Appendix L Instruments Used During MLN0002-3024

Instrument	Completed By	Device Used	Mode
Tanner staging	Clinician	iPad [a]	ClinRo
PUCAI	Clinician	iPad [a]	ClinRo
Complete Mayo score	Calculation	NA	NA
Partial Mayo score	Calculation	NA	NA
Modified Mayo score	Calculation	NA	NA
PGA for Mayo score completion	Clinician	iPad [a]	ClinRo
Endoscopy ClinRO question	Clinician	iPad [a]	ClinRo
Electronic diary	Subject/Caregiver	iPhone [b]	SRO
IMPACT-III	Subject	iPad [c]	SRO

ClinRo: clinician-reported outcome; NA: not applicable; PGA: Physician's Global Assessment; PUCAI: Pediatric Ulcerative Colitis Activity Index; SRO: subject-reported outcome.

[a] Site iPad will be used.

[b] Subjects will be provided an iPhone for use to complete their daily diaries during the study.

[c] Subject will enter responses to the IMPACT-III questionnaire using the site iPad during their clinic visits.

Appendix M Protocol History

Date	Amendment Number	Region
27 February 2025	7	Global
19 September 2024	6	Global
03 July 2024	5	Global
08 September 2023	4	Global
28 November 2022	3	Global
13 October 2021	2	Global
16 February 2021	1	Global
14 October 2020	Initial version	Global

Protocol Amendment 6 Summary and Rationale.

This section describes the changes in reference to the protocol incorporating Amendment No. 6. The primary reasons for this amendment are to:

- Fix all formatting, editorial, and administrative issues for clarity.
- Update record retention policy.
- Harmonize serious infections adverse event of special interest (AESI) definition across the vedolizumab program.

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*
5.	Investigator Agreement	'Section 10.1' is updated to 'Section 10.2'	Correction.
6.	Section 2.0 STUDY SUMMARY	Removed all hyperlinks.	For consistency.
7.	Section 2.0 STUDY SUMMARY	Administrative changes have been made to the efficacy analysis section.	Repetitive information has been removed, as the content is covered in Section 13.1.3 Efficacy Analysis.
8.	Section 6.1 Study Design	Hyperlinking is corrected.	For clarification.
9.	Section 6.1 Study Design	Repetitive text 'to one of the 2 dose groups (high dose, low dose),' is deleted.	Correction.

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***
10.	Section 7.1 Inclusion Criteria Section 7.2 Exclusion Criteria	Indentation to numbering is updated for both sections.	For clarification.
11.	Throughout amendment	Minor editorial changes (eg, fixing hyphens, capitalization, spacing, spelling, bullets, periods, indentation etc.) are updated.	For consistency.
12.	Section 10.2.1.3 AESIs	Revised the statement from 'Severe infection (see Section 10.1.6) or infections that meet seriousness criteria will be reported as AESIs' to 'Infections that meet seriousness criteria will be reported as AESIs'.	Revised for consistency across the vedolizumab program.
13.	Section 12.2 Record Retention	Revised the statement from 'The investigator agrees to keep the records stipulated in Section 12.1 for 25 years after study completion and those documents that include (but are not limited to) the study-specific documents' to ''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'	Revised for consistency across the vedolizumab program.
14.	Section 13.1 Statistical and Analytical Plans	'Study vedolizumab' is replaced with 'study drug'.	Clarification
15.	Section 13.1.3 Efficacy Analysis	Definitions have been added for negative antivedolizumab antibody (AVA), positive AVA, and neutralizing AVA (nAVA) status.	Ensure consistency across the vedolizumab program.

Protocol Amendment 5 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 5. The primary reasons for this amendment are to:

— Comply with European Union (EU) Clinical Trial Regulation (CTR) protocol requirements.

— Update Interim Analysis section.

— Update Treatment-emergent Adverse Events (TEAEs) definition.

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 5			
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.	Title Page	Sponsor Address was updated.	
2.	Contacts	Contact information was updated and consolidated for ease of use.	
3.	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.
4.	Signatures	The names of the responsible Takeda medical officer and other signatories were updated.	
5.	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.
6.	Section 3.1 Study-Related Responsibilities	Revised study-related responsibilities.	Revised for clarity.
7.	Section 3.5 Study Definitions	Definitions of 'Study start' and 'Enrollment' were added.	To comply with EU CTR protocol requirements.
8.	Section 4.1.3 Vedolizumab Intravenous	Revised 'over 71 countries' to 'more than 70 countries' in the Subsection 4.1.3.2 Clinical.	Revised for clarity.
9.	Section 2.0 Study Summary Section 4.6 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.
10.	Section 4.3 Rationale for Auxiliary Medicinal Products for Rescue Treatment Section 4.5 Risks Associated With AxMPs Section 10.3 Follow-Up of SAEs	The sections pertaining to defining, identifying and reporting EU authorized/unauthorized auxiliary medicinal products were added.	To comply with EU CTR protocol requirements.

Protocol Amendment 5			
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***
	Section 16.0 References Appendix B AxMPs		
11.	Figure 6.a Schematic of Study Design	Added 'see Section 9.2.5' in parentheses to footnote 'f'.	Revised for clarity.
12.	Section 7.3 Excluded Medications and/or 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 UC 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 period would be permitted or not.
13.	Section 7.6 Procedures for Discontinuation or Withdrawal of a Subject	The relevant subsections explaining the procedures for the 'subjects who withdraw/discontinue from the study' were added.	To comply with EU CTR protocol requirements.
14.	Section 9.1 Study Procedures	Revised the demographic information that will be collected at screening.	Revised for clarity and to comply with EU CTR protocol requirements.
15.	Section 9.1 Study Procedures	Revised procedure for physical examination.	Clarification.
16.	Section 9.1 Study Procedures Appendix G Approximate Blood Volume (mL)	o Revised the blood volume collected for chemistry (including C-reactive protein) analysis for subjects weighing ≥30 kg at Week 54/end-of-study/early termination visit, follow-up safety visit and the approximate total volume of blood collected for the study. o The following statement, 'These are estimated blood volumes. Please refer to the central and local laboratory-provided documents for	Correction and clarification.

Protocol Amendment 5			
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***
		the specific blood volumes collected by these laboratories.' was added in the footnote of the table.	
17.	Section 9.2 Schedule of Observations and Procedures	Revised the statement from, 'The study drug will not be available upon completion of the subject's participation in the study unless posttrial access program is available depending on country specific requirements' to 'Study drug will not be available upon completion of the subject's participation in the study except in countries where other drug access programs become available'.	Revised for clarity.
18.	Section 10.0 PTE and AE	A table titled, 'AE Subtypes defined in this section' was added.	To comply with EU CTR protocol requirements.
19.	Section 10.3 Follow-Up of SAEs	The subsection on reporting of special situations was added.	To comply with EU CTR protocol requirements.
20.	Section 10.3 Follow-Up of SAEs	The requirements for suspected unexpected serious adverse reaction reporting were updated.	To comply with EU CTR protocol requirements.
21.	Section 12.2 Record Retention Section 12.3 Sample Retention and Use Section 15.2 Subject Information, Informed Consent, and Subject Authorization	The details about procedures for collection storage, record retention and future use of biological samples were added.	To comply with EU CTR protocol requirements.
22.	Section 2.0 Study Summary Section 3.5 Study Definitions Section 13.1 Statistical and Analytical Plans	Revised TEAEs definition.	Revised for clarity.
23.	Section 13.1 Statistical and Analytical Plans	An additional statement, 'If not otherwise mentioned, continuous variables will be summarized using descriptive statistics (number of subjects,	Added for clarity.

Protocol Amendment 5			
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***
		mean, SD, minimum, median, and maximum) and categorical variables will be summarized by frequency tables showing the number and proportion of subjects falling into each category.' was added.	
24.	Section 13.2 IA and Criteria for ET	Revised interim analysis and criteria for early termination.	Revised for clarity.
25.	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.
26.	Appendix C Responsibilities of the Investigator	An additional point, '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.' was added.	Added for clarity.
27.	Appendix D 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.

Protocol Amendment 4 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 4. The primary reasons for this amendment are to:

— Incorporate follow-up of all pregnancies and pregnancy outcomes for 1 year after birth.

— Clarify Tanner scale procedures.

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 4			
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	Deleted sentence "No comparisons between dose arms will be made."	Deletion of inaccurate statement.
2.	Section 2.0 STUDY SUMMARY Section 5.2.2 Secondary Endpoints Section 13.1.3 Efficacy Analysis	Clarified Tanner scale endpoints and procedures.	Clarification in analysis to control for different Tanner stages at enrollment.
3.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Section 7.3.1.1.2 Corticosteroid Rescue Treatment Section 7.6 Procedures for Discontinuation or Withdrawal of a Subject Section 9.2.5 Poststudy Care	Deleted 'then be eligible' from "Subjects will then be eligible to enter Study MLN0002-3029 for an observational long-term follow-up (LTFU) period of 2 years after the last dose of study drug"	Change made to ensure subjects enter the observational period of Study MLN0002-3029.
4.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Section 7.3.1.1.2 Corticosteroid Rescue Treatment Section 7.6 Procedures for Discontinuation or Withdrawal of a Subject Section 9.2.5 Poststudy Care	Added mention of possibility for phone calls to subject's health care provider, rather than clinic visits, every 6 months as part of LTFU in Study MLN0002-3029.	Revised explanation of procedures in Study MLN0002-3029 to align with changes made in MLN0002-3029 Protocol Amendment 2.
5.	Section 9.1.6 Primary Efficacy Measurement Appendix G Scoring System for the Assessment of Ulcerative Colitis Activity	Modified language for the ulcerative colitis activity assessment.	Change made to align with Takeda internal processes.
6.	Section 9.1.11 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.
7.	Poststudy Care	Included mention of subjects need to be <18 years of age to enter the treatment portion of Study MLN0002-3029.	Change made to clarify that subjects ≥18 years of age have the option to enter the observational portion of Study

Protocol Amendment 4			
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***
			MLN0002-3029.
8.	Section 13.1.1 Analysis Sets	Deleted intent-to-treat (ITT)-induction (I).	Correction – the ITT-I includes the same population as the ITT.
9.	Section 13.2 IA and Criteria for ET	Removed specific mention of high weight group from potential interim analysis.	Deleted to allow capture of all available information, including data from subjects in the low weight group, at the time of a potential interim analysis.

Protocol Amendment 3 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 3. The primary reasons for this amendment are to:

— Extend the screening period.

— Remove the poststudy LTFU safety survey telephone calls from this study.

— Improve consistency between objectives and endpoints.

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 3			
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	Modified "Period of Evaluation" to reflect maximum period of evaluation.	Revised to remove the observational long-term follow-up (LTFU) period and define the end of study as 18 weeks after the last dose of study drug.
2.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design	Clarified that randomization will be 1:1 for the high and low dose for each weight group.	Linguistic clarification.
3.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Figure 6.a Schematic of Study Design Section 9.2.1 Screening	Extended the screening period from 28 to 35 days.	Screening period extended to ensure laboratory assessment results are available from central laboratory for investigator evaluation before performing a screening colonoscopy. This reduces risk that an invasive procedure is

Protocol Amendment 3			
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***
	Appendix A Schedule of Study Procedures		performed on a subject who would otherwise be ineligible based upon exclusionary laboratory results.
4.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Figure 6.a Schematic of Study Design Section 7.3.1.1.2 Corticosteroid Rescue Treatment Section 7.6 Procedures for Discontinuation or Withdrawal of a Subject Section 9.2.5 Poststudy Care Section 10.2.1.1 PTE and AE Collection Period Appendix A Schedule of Study Procedures	Removed the poststudy LTFU safety survey telephone calls.	Revised to allow more thorough assessment of the LTFU period by separating it from the interventional portion of this study. Observational LTFU assessments will be included as part of the open-label extension study MLN0002-3029.
5.	Section 2.0 STUDY SUMMARY Section 5.0 STUDY OBJECTIVES AND ENDPOINTS Section 13.1.3 Efficacy Analysis	Modified several objectives and endpoints.	Changes made to improve alignment between objectives and endpoints.
6.	Section 2.0 STUDY SUMMARY Section 9.1.6 Primary Efficacy Measurement Section 9.1.6 Primary Efficacy Measurement	Specified that modified Mayo score should be assessed before infusion of study drug.	Revised to ensure the sequence of assessments and procedures is unambiguous.
7.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria Section 9.1.6 Primary Efficacy Measurement	Clarified need for screening endoscopy to assess disease severity.	Revised for clarity.
8.	Section 4.1.3.2 Clinical	Revised Study C13008 antivedolizumab antibodies (AVA) data.	Corrected erroneous text.
9.	Section 4.1.3.2 Clinical Section 4.3 Benefit-Risk Profile	Revised vedolizumab introductory content.	Changes made to improve the organization of these sections

Protocol Amendment 3			
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***
			and to replace references to documents unavailable to health authorities with references to documents that are available.
10.	Section 4.1.3.2 Clinical Section 10.2.1.3 AESIs	Relocated information on progressive multifocal leukoencephalopathy (PML) status to adverse events of special interest (AESI) section and added information about known cases of PML in patients taking vedolizumab.	Revised to place information in a more relevant location in the protocol.
11.	Section 7.2 Exclusion Criteria	Revised hepatitis B virus (HBV) and hepatitis C (HBC) exclusion criteria.	Change made to clarify the criteria to be used to define subjects who are HBV and HBC immune.
12.	Section 7.3 Excluded Medications and/or Procedures, and Treatments	Identified additional excluded medications.	Change made to update the list of medications that could potentially be used in pediatric subjects (eg, off-label) but are not permitted together with vedolizumab.
13.	Section 7.3.1.1.1 Corticosteroids During Screening and Induction	Clarified acceptable corticosteroid use during screening.	Revised to reduce ambiguity.
14.	Section 7.3.1.1.1 Corticosteroids During Screening and Induction	Excluded initiation of corticosteroids during induction as well as screening.	Change made to avoid biased evaluation of treatment response at Week 14 as corticosteroids could facilitate treatment response.
15.	Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject	Included examples of AESIs of hypersensitivity reaction or newly diagnosed malignancy are included as possible reasons for subject discontinuation or withdrawal.	Clarified that these AESIs, not included elsewhere in the criteria for subject discontinuation or withdrawal, are now included.
16.	Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject	Added discontinuation criterion for any subject whose weight decreases to <10 kg during the study and is confirmed at 2 consecutive visits (scheduled or unscheduled) at least 7 days apart.	Change made to maintain consistency with minimum body weight specified as an inclusion criterion and reduce the risk of collected blood volume potentially exceeding maximum recommended per

Protocol Amendment 3			
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			guidelines. Additionally, 10 kg (third percentile for a 2-year-old per the Centers for Disease Control growth chart) is the lowest weight evaluated in phase 2 vedolizumab studies as well as pharmacokinetics (PK) exposure simulations.
17.	Section 9.1.6 Primary Efficacy Measurement	Quantified expected diary compliance.	Change made to ensure compliance in diary completion
18.	Section 9.1.6 Primary Efficacy Measurement Section 9.1.20 Endoscopies Appendix A Schedule of Study Procedures	Clarified timing for screening endoscopy and the timing and assessment of modified Mayo score.	Change made to ensure enough diary entries are available before endoscopy is performed and enough time for the endoscopy score to be reported.
19.	Section 9.1.9 Procedures for Clinical Laboratory Samples Table 9.a Clinical Laboratory Tests Section 9.1.15 Fecal Calprotectin Sample Collection Section 9.1.16 Stool Sample for Culture, Ova and Parasite Evaluation, and *C difficile* Assay Appendix A Schedule of Study Procedures	Revised to allow screening and unscheduled visit stool tests (with the exception of fecal calprotectin) to be performed locally.	Change made to enable a more rapid turnaround time for these tests.
20.	Section 9.1.21 Documentation of Screen Failure	Revised screen failure language.	Corrected to align with standards.
21.	Section 9.2.7 Other Unscheduled Visits (if Applicable) Appendix A Schedule of Study Procedures	Added complete and modified Mayo scores, and endoscopy, all at the investigator's discretion, to unscheduled visit assessments.	Change made to allow calculation of modified and complete Mayo scores in the event of an unscheduled endoscopy performed at the investigator's discretion.
22.	Section 9.2.7 Other Unscheduled Visits (if Applicable) Appendix A Schedule of Study Procedures	Added AVA and PK to unscheduled visit assessments.	Change made evaluate the effect of AVA on study-related adverse events.
23.	Section 10.1.3 Additional Points to Consider for PTEs and AEs	Removed references to electronic case report form	Changes made to accurately reflect the actual eCRF.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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	Section 10.2.3 Reporting of Abnormal Liver Associated Tests	(eCRF) pages that do not exist for this study.	
24.	Section 10.1.12 Action Concerning Study Drug	Revised possible actions concerning study drug.	Changes made to maintain consistency with study design.
25.	Section 13.1.1 Analysis Sets	Clarified the induction and maintenance analysis sets.	Change made to align with Statistical Analysis Plan (SAP), version 2.
26.	Section 13.1.4 PK Analysis	Removed reference to Clinical Pharmacology Data Analysis Plan and replaced with reference to standalone report of PK analysis and results.	Corrected to reflect analysis plan details to be part of the standalone report.
27.	Appendix A Schedule of Study Procedures	Clarified footnote b in the Schedule of Study Procedures.	Change made to clarify which assessments are required for unscheduled visits for disease exacerbation vs assessments that may be performed at the investigator's discretion during unscheduled visits performed for other reasons.

Protocol Amendment 2 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 2. The primary reasons for this amendment are to:

— Allow for dose escalation based on weight at the time of disease worsening.

— Clarify contraception language.

— Update blood volumes.

— Align endpoints and objectives.

— Change the PUCAI from a secondary to an exploratory endpoint.

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 2			
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 3.5 Study Definitions Section 6.1 Study Design	Removed PUCAI from the definitions of clinical response at Week 14 and disease worsening so that randomization in the maintenance phase will be based solely on modified Mayo score.	Revised to align the instrument used for definition of clinical response at Week 14 with the one used for primary endpoint assessment. The sample size was calculated on response rate in phase 2 study MLN0002-2003, which was based only on complete or partial Mayo scores, thus also risking lower response rate if the combination of Mayo/PUCAI was kept.
2	Section 2.0 STUDY SUMMARY Section 3.5 Study Definitions Section 6.1 Study Design	Revised definition of clinical response at Week 14 to be based on modified Mayo score.	Change made to account for inclusion of the Mayo endoscopic score as part of the definition of clinical response at Week 14.
3	Section 2.0 STUDY SUMMARY Section 3.5 Study Definitions Section 6.1 Study Design	Removed PUCAI from the definition of worsening of disease so that dose escalation will be based solely on modified Mayo score.	Revised to align the new proposed definition of clinical response at Week 14 with the primary efficacy endpoint for clinical response at Week 54.
4	Section 2.0 STUDY SUMMARY Section 5.0 STUDY OBJECTIVES AND ENDPOINTS Section 13.1 Statistical and Analytical Plans	Added details to objectives and endpoints.	Revised to clarify and align with existing objectives and endpoints.
5	Section 2.0 STUDY SUMMARY Section 5.1.3 Exploratory Objectives Section 5.2 Endpoints Section 13.1 Statistical and Analytical Plans	Added PUCAI as a measure of clinical response and remission in exploratory objectives; downgraded PUCAI from secondary efficacy endpoint to exploratory.	PUCAI score does not include endoscopic evaluation of mucosal healing. This change is consistent with similar approach used in other pivotal clinical trials in pediatric UC.
6	Section 2.0 STUDY SUMMARY	Allowed dose escalation for subjects in the low-weight	Dose escalation in subjects who lose response while

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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	Section 6.1 Study Design	groups (<30 kg) based on weight at the time of disease worsening for subjects assigned to the high dose (currently dose escalation only allowed for subjects assigned to the low dose).	changing weight group offers the possibility of regaining response to the new corresponding weight group dose.
7	Section 2.0 STUDY SUMMARY Section 6.1 Study Design	Removed language about "dose escalation for worsening of disease will occur at the next infusion."	Waiting 8 weeks for the next infusion would limit the value of dose escalation and may increase discontinuation or risk of starting a prohibited drug to treat worsening of disease. Dose escalation will occur at the time disease worsening is reported.
8	Section 2.0 STUDY SUMMARY Section 7.3.1.1 Oral Corticosteroid Dosing	Added a specific paragraph for corticosteroid rescue treatment.	Revised to provide clarifications about corticosteroid rescue therapy and tapering during maintenance phase.
9	Section 2.0 STUDY SUMMARY Section 13.1.3 Efficacy Analysis	Specified dilution factors used for antivedolizumab antibodies (AVA) analysis.	Change made to clarify AVA analysis methodology.
10	Section 3.5 Study Definitions	Updated the definition of end of study (EOS) (currently last subject completing Week 54) to be last subject, last visit (inclusive of the follow-up safety visit for subjects who do not enter the MLN0002-3029 extension study).	Revised to ensure consistency with Takeda standard and alignment with European Union CT-1 guidance.
11	Section 6.1 Study Design (Figure 6.a) Section 7.6 Procedures for Discontinuation or Withdrawal of a Subject Appendix A	Removed requirement, upon early discontinuation from the study to complete procedures if those procedures had already been recently completed.	Removed requirement to repeat procedures already performed as part of a scheduled visit, if discontinuation occurs in close proximity of such visit.
12	Section 6.1 Study Design Section 9.1.6 Primary Efficacy Measurement Section 9.1.17 PUCAI Section 9.1.18 IMPACT-III	Added Appendix J to describe the instruments used in this study.	Clarified the use and timing of instruments in this study.

Protocol Amendment 2			
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***
	Questionnaire—Subjects 9 to 17 Years of Age Appendix J		
13	Section 7.1 Inclusion Criteria Section 9.1.10 Contraception and Pregnancy Avoidance Procedure	Removed provision for "effective contraception methods" to only allow for "highly effective methods."	Revised to align with Clinical Trials Facilitation and Coordination Group recommendations related to contraception in clinical trials.
14	Section 7.2 Exclusion Criteria	Added exclusion criteria for heart failure or other medical disorder, clinical laboratory results, malignancy, and psychiatric conditions that may confound study results or compromise subject safety.	Added to allow for the exclusion of patients who may pose safety concerns during the conduct of the study and to enable early discontinuations due to safety reasons. Revision is consistent with other vedolizumab trials, including the phase 2 pediatric study.
15	Section 9.1.9 Procedures for Clinical Laboratory Samples Section 9.1.10 Contraception and Pregnancy Avoidance Procedure Appendix A Appendix E	Added requirement of pregnancy test in all female subjects who are menstruating (regardless of age) or are aged ≥11years; currently only performed if subject had reached menarche.	Irregular periods are common in adolescents with IBD.
16	Section 9.1.9 Procedures for Clinical Laboratory Samples Appendix A	Removed erythrocyte sedimentation rate from laboratory tests.	C-reactive protein has been shown to be superior to erythrocyte sedimentation rate in reflecting disease activity in pediatric subjects with ulcerative colitis (UC) and more closely correlated with endoscopic appearance; therefore, it is not necessary to perform both tests.
17	Section 9.1.9 Procedures for Clinical Laboratory Samples Appendix E	Updated blood volumes needed for pharmacokinetic analysis.	Revised to align with Clinical Biomarker Innovation and Development requirement.
18	Section 9.1.9 Procedures for Clinical Laboratory Samples Appendix E	Introduced tuberculin skin test for screening as an alternative to QuantiFERON (currently mentioned in the inclusion and exclusion criteria but not in the	Updated the section of procedures performed to make it consistent with the inclusion and exclusion criteria.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
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		procedures).	
19	Section 9.1.10 Contraception and Pregnancy Avoidance Procedure	Removed eligibility requirement for confirmed menses in the month before first dosing.	Delayed menses are common in adolescents with inflammatory bowel disease (IBD), and pregnancy tests will be performed at screening and before each dosing.
20	Appendix A	Visit window for Week 14 and Week 54 extended to ±7 days.	Change made to allow enough time to collect centrally read results for the endoscopy.
21	Appendix E	Updated blood volume table to reduce the maximum amount of blood to be drawn in a single visit.	Removed discrepancy with central lab manual.
22	Appendix H	Revised PUCAI content in the applicable appendix.	Change made to reflect the latest version provided by the author.

Protocol Amendment 1 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 1. The primary reasons for this amendment are to:

— Clarify the length of vedolizumab infusion for subjects weighing <20 kg to align with instructions in the phase 2 study protocols (MLN0002-2003 and Vedolizumab-2005) and to ensure that potential exposure to endotoxin during infusion is within the margin of safety.

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 1			
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 8.1.3 Dose and Regimen	Added information defining the duration of vedolizumab infusion, specifying a 2-hour infusion for subjects weighing <20 kg.	This modification will ensure that low weight subjects are not potentially at risk of exposure to unsafe levels of endotoxin.
2	Section 9.1.7 IMPACT-III Questionnaire—Subjects 9 to 17 Years of Age	Deleted "Questionnaire entries will be transcribed by site personnel into the eCRF."	This information will not be recorded in the electronic case report form (eCRF).

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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3	Appendix A Schedule of Study Procedures	Added information to footnote "a" to delineate when subjects may be eligible to enter the extension study and to clarify that the long-term follow-up (LTFU) visit includes only the safety survey phone call.	Clarifications.

Signature Page for MLN0002-3024 Protocol Amend #7 2025-Feb

Title: Amendment 7 of A Randomized, Double-Blind, Phase 3 Study to Evaluate the

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