



Clinical Study Protocol

NCT Number: NCT04738942

Title: An Open-Label, Phase 3 Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Intravenous (IV) Vedolizumab Administered Every 4 Weeks (Q4W) in Japanese Patients with Moderate to Severe Ulcerative Colitis or Crohn's Disease who Experienced Secondary Loss of Response During Maintenance Therapy with Vedolizumab IV Administered Every 8 Weeks (Q8W)

Study Number: Vedolizumab-3039

Document Version and Date: Amendment 2 / 04 OCT 2024

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

A summary of changes to previous protocol versions is appended to the end of the document.

TAKEDA PHARMACEUTICALS

PROTOCOL

An Open-Label, Phase 3 Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Intravenous (IV) Vedolizumab Administered Every 4 Weeks (Q4W) in Japanese Patients with Moderate to Severe Ulcerative Colitis or Crohn's Disease who Experienced Secondary Loss of Response During Maintenance Therapy with Vedolizumab IV Administered Every 8 Weeks (Q8W)

Phase 3 Study of Intravenous (IV) Vedolizumab Administered Every 4 Weeks (Q4W) in Japanese Patients with Moderate to Severe Ulcerative Colitis or Crohn's Disease

Sponsor: Takeda Pharmaceutical Company Limited
1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka, Japan

Study Number: Vedolizumab-3039

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Compound: Vedolizumab IV

Date: 04 October 2024 **Version/Amendment Number:** Amendment 02

Amendment History

Date	Amendment Number	Amendment Type	Region
07 December 2020	Initial Version	Not applicable	All sites
27 January 2022	01	Substantial	All sites
04 October 2024	02	Substantial	All sites

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1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

A separate contact information list will be provided to each site (see the annexes).

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1.2 Principles of Clinical Studies

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 Council for Harmonisation E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.
- "Ministerial Ordinance Concerning the Standards for the Conduct of Clinical Trials of Medicinal Products" (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 28, 27 March 1997; hereinafter referred to as "the GCP Ordinance").
- "The Ministerial Ordinance that Partially Revises the Ministerial Ordinance Concerning the Standards for the Conduct of Clinical Trials of Medicinal Products" (hereinafter referred to as "the revised GCP Ordinance").
- Pharmaceutical Affairs Law.

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.

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Head, Medical Franchise Gastroenterology		Biostatistics	

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1.3 Protocol Amendment 02 Summary of Changes

This document describes the changes in reference to the protocol incorporating Amendment 02.

The primary reasons for this amendment are to:

- To allow for the final analysis with ≥ 31 subjects in the UC cohort, added re-estimated sample size and criteria to conclude statistical significance at final analysis for the primary endpoint.
- To allow for the final analysis with ≥ 15 subjects in the CD cohort, added precision of estimation based on 15 subjects.

The following is a summary of the changes made in this amendment.

Protocol Amendment 02		
Summary of Changes		
Section(s) Affected by Change	Description of Each Change and Rationale	
Location	Description	Rationale
Section 2.0 Study Summary, Number of Subjects, Statistical Considerations Section 13.1.3.1 Primary Efficacy Analysis Section 13.2 Interim Analysis and Criteria for Early Termination	Added Table 13-c Re-estimated Sample Size and Criteria to Conclude Statistical Significance at Final Analysis for the Primary Endpoint ($N \geq 31$). Added that the criteria are statistically appropriate.	To allow for the final analysis with ≥ 31 subjects in the UC cohort.
Section 2.0 Study Summary, Number of Subjects, Sample Size Justification Section 13.3 Determination of Sample Size	Added precision of estimation based on 15 subjects in the CD cohort.	To allow for the final analysis with ≥ 15 subjects in the CD cohort.

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited		Compound: Vedolizumab IV	
Title of Protocol: An Open-Label, Phase 3 Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Intravenous (IV) Vedolizumab Administered Every 4 Weeks (Q4W) in Japanese Patients with Moderate to Severe Ulcerative Colitis or Crohn's Disease who Experienced Secondary Loss of Response During Maintenance Therapy with Vedolizumab IV Administered Every 8 Weeks (Q8W)		IND No.: Not Applicable	EudraCT No.: Not Applicable
Study Number: Vedolizumab-3039		Phase: 3	
<p>Study Design:</p> <p>This is a phase 3, multicenter, open-label, single-arm study to evaluate the efficacy, safety, and pharmacokinetics (PK) of vedolizumab IV Q4W in Japanese subjects with moderate to severe ulcerative colitis (UC) or Crohn's disease (CD), who experienced secondary loss of response during maintenance therapy with commercially available vedolizumab IV Q8W. This study consists of screening, treatment, and extension phases.</p> <p>Subjects meeting the eligibility criteria based on the inclusion and exclusion criteria on the first day of treatment (Day 1) will be enrolled into the treatment phase and will receive vedolizumab 300 mg IV at Weeks 0, 4 and 8. The interval between the last dose of commercially available vedolizumab IV and Day 1 must be within the range of 4 to 8 weeks. The primary efficacy evaluation will be performed at Week 12.</p> <p>Subjects showing a clinical response at Week 12 can enter into the extension phase and can continue to receive vedolizumab IV starting from Week 12 and then every 4 weeks in an unblinded manner, until the date of marketing approval of vedolizumab IV Q4W, study termination, or subject withdrawal. Subjects not showing a clinical response at Week 12 will discontinue the study at Week 12 (considered as Week 12 completers with non-response). The end-of-study examination will be performed at 16 weeks after the last dose in subjects who received the study drug. Additionally, the follow-up safety-survey by telephone is to be performed 6 months after the last dose of study drug.</p> <p>Endoscopy will be performed in the rectum and sigmoid colon at screening and at Week 12 or early termination (ET) for the UC cohort. All endoscopies will be centrally read. Inclusion into the treatment phase (at Week 0) will be decided based on the central reader's assessment, while enrollment into the extension phase (at Week 12) will be decided based on the investigator's assessment. Efficacy analyses will be performed using Mayo endoscopic subscore assessed by the central reader. Endoscopy will not be performed for the CD cohort.</p> <p>For the UC cohort, an interim analysis (IA) will be performed when the first 30 subjects complete assessments at Week 12 or ET. Based on the outcome of IA, a decision will be made on either of efficacy stopping, futility stopping, or study continuation with sample size re-estimation.</p>			
<p>Primary Objective:</p> <p>To assess the effect of vedolizumab IV Q4W on clinical response at Week 12 in Japanese subjects with moderate to severe UC or CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.</p>			
<p>Secondary Objectives:</p> <ul style="list-style-type: none"> To assess the safety of vedolizumab IV Q4W in Japanese subjects with moderate to severe UC or CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W. 			

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<p><u>UC cohort</u></p> <ul style="list-style-type: none"> To assess the effect of vedolizumab IV Q4W on clinical remission based on modified Mayo score at Week 12 in Japanese subjects with moderate to severe UC who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W. To assess the effect of vedolizumab IV Q4W on mucosal healing based on Mayo endoscopic subscore at Week 12 in Japanese subjects with moderate to severe UC who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W. To assess the effect of vedolizumab IV Q4W on corticosteroid-free remission based on partial Mayo score at Week 52 in Japanese subjects with moderate to severe UC who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W and achieved clinical response at Week 12. <p><u>CD cohort</u></p> <ul style="list-style-type: none"> To assess the effect of vedolizumab IV Q4W on clinical remission based on Crohn's Disease Activity Index (CDAI) at Week 12 in Japanese subjects with moderate to severe CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W. To assess the effect of vedolizumab IV Q4W on enhanced clinical response based on CDAI at Week 12 in Japanese subjects with moderate to severe CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W. To assess the effect of vedolizumab IV Q4W on corticosteroid-free remission based on CDAI at Week 52 in Japanese subjects with moderate to severe CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W and achieved clinical response at Week 12. 	
<p>Subject Population:</p> <p>Japanese subjects aged 18 to 80 years, inclusive, with moderate to severe UC or CD who experienced secondary loss of response during maintenance therapy with commercially available vedolizumab IV Q8W.</p>	
<p>Number of Subjects:</p> <p><u>UC cohort</u></p> <p>60 subjects are planned to be enrolled into the study. An IA will be performed when the first 30 subjects complete assessments at Week 12 or ET. If the decision at the IA is either efficacy or futility stopping, then further enrollment for the UC cohort will be stopped. If the decision is to continue the study, then the total sample size may be re-estimated to a maximum of 135. In addition, UC cohort may be completed with any number of subjects greater than or equal to 31 subjects and then final analysis will be performed.</p> <p><u>CD cohort</u></p> <p>A total of 23 subjects will be enrolled into the study. In addition, CD cohort may be completed with any number of subjects greater than or equal to 15 subjects and then final analysis will be performed.</p>	<p>Number of Sites:</p> <p>Estimated total: 20 sites in Japan</p>
<p>Dose Level:</p> <p>Vedolizumab 300 mg</p>	<p>Route of Administration:</p> <p>IV infusion</p>

<p>Duration of Treatment:</p> <p>Treatment phase: 12 weeks</p> <p>Extension phase: until the date of marketing approval of vedolizumab IV Q4W or study termination</p>	<p>Period of Evaluation:</p> <p>Treatment phase: 12 weeks</p> <p>Extension phase: until the date of marketing approval of vedolizumab IV Q4W or study termination</p>
<p>Main Criteria for Inclusion:</p> <p><u>UC cohort</u></p> <ol style="list-style-type: none"> The subject has moderate to severe UC, who had previously shown clinical response* in initial treatment with commercially available vedolizumab IV, then experienced secondary loss of response** during maintenance therapy with commercially available vedolizumab IV Q8W. <p>*Previous “clinical response” is to be judged by the investigators referring to one of the following criteria.</p> <ul style="list-style-type: none"> Reduction of ≥ 2 points and $\geq 25\%$ in modified Mayo score, and a decrease of ≥ 1 point in rectal bleeding subscore or rectal bleeding subscore of ≤ 1, from the start of initial treatment with commercially available vedolizumab IV. Reduction of ≥ 2 points and $\geq 25\%$ in partial Mayo score, and a decrease of ≥ 1 point in rectal bleeding subscore or rectal bleeding subscore of ≤ 1, from the start of initial treatment with commercially available vedolizumab IV. Significant improvement on endoscopy (i.e., a decrease of ≥ 2 points in Mayo endoscopic subscore). <p>** “Secondary loss of response” is to be judged by the investigators referring to one of the following criteria.</p> <ul style="list-style-type: none"> Increase of ≥ 2 points in modified Mayo score, and an increase of ≥ 1 point in rectal bleeding subscore or rectal bleeding subscore ≥ 2, from the start of maintenance therapy with commercially available vedolizumab IV. Increase of ≥ 2 points in partial Mayo score, and an increase of ≥ 1 point in rectal bleeding subscore or rectal bleeding subscore ≥ 2, from the start of maintenance therapy with commercially available vedolizumab IV. Significant deterioration on endoscopy (i.e., an increase of ≥ 2 points in Mayo endoscopic subscore). <ol style="list-style-type: none"> The subject has active UC as determined by a modified Mayo score of ≥ 5 at baseline (within 10 days prior to the start of treatment phase) with a Mayo rectal bleeding subscore of ≥ 1 at baseline (within 10 days prior to the start of treatment phase) and a Mayo endoscopic subscore of ≥ 1 as assessed by the central reader. <p><u>CD cohort</u></p> <ol style="list-style-type: none"> The subject has moderate to severe CD, who had previously shown clinical response* in initial treatment with commercially available vedolizumab IV, then experienced secondary loss of response** during maintenance therapy with commercially available vedolizumab IV Q8W. <p>*Previous “clinical response” is to be judged by the investigators referring to one of the following criteria.</p> <ul style="list-style-type: none"> Reduction of ≥ 70 points in CDAI score from the start of initial treatment with commercially available vedolizumab IV. 	

- Reduction of ≥ 3 points in Harvey-Bradshaw Index (HBI) score from the start of initial treatment with commercially available vedolizumab IV.
- ** “Secondary loss of response” is to be judged by the investigators referring to one of the following criteria.
- Increase of ≥ 70 points in CDAI score from the start of maintenance therapy with commercially available vedolizumab IV.
 - Increase of ≥ 3 points in HBI score from the start of maintenance therapy with commercially available vedolizumab IV.
2. The subject has active CD as determined by a CDAI score of ≥ 220 at baseline (within 10 days prior to the start of treatment phase).
 3. The subject has a C-reactive protein C-reactive protein (CRP) level >3.0 mg/L during the screening phase.

Main Criteria for Exclusion:

1. The subject has had extensive colonic resection, subtotal or total colectomy.
2. The subject has received any of the investigational or approved non-biologic therapies (e.g., cyclosporine, tacrolimus or tofacitinib, except for those specifically listed as permitted medications) for the treatment of underlying disease within 30 days or 5 half-lives of screening (whichever is longer).
3. The subject has received any investigational or approved biologic or biosimilar agent other than vedolizumab IV within 60 days or 5 half-lives of screening (whichever is longer).
4. The subject has a clinically significant active infection (e.g., pneumonia, pyelonephritis or coronavirus disease 2019 [COVID-19]) within 30 days prior to screening or during screening, or has an ongoing chronic infection, or has lingering COVID-19-related symptoms, if previously infected with COVID-19.
5. The subject has known or suspected intolerance or hypersensitivity to vedolizumab or closely related compounds, or any of the vedolizumab IV excipients.
6. The subject has active cerebral/meningeal disease, or signs/symptoms of progressive multifocal leukoencephalopathy (PML) or any history of PML at screening.

Main Criteria for Evaluation and Analyses:

Primary endpoint:

UC cohort

- Proportion of subjects with clinical response at Week 12 based on modified Mayo score, defined as a reduction of ≥ 2 points and $\geq 25\%$ in modified Mayo score, and a decrease of ≥ 1 point in rectal bleeding subscore or rectal bleeding subscore of ≤ 1 from baseline (Week 0).

CD cohort

- Proportion of subjects with clinical response at Week 12, defined as a reduction of ≥ 70 points in CDAI score from baseline (Week 0).

Secondary endpoints:

UC cohort

- Proportion of subjects with clinical remission at Week 12 based on modified Mayo score, defined as a modified Mayo score of ≤ 2 , and no individual subscore >1 .

- Proportion of subjects with mucosal healing at Week 12, defined as a Mayo endoscopic subscore of ≤ 1 , in subjects with baseline Mayo endoscopic subscore of ≥ 2 .
- Proportion of subjects with corticosteroid-free remission based on partial Mayo score, defined as subjects using oral corticosteroids at baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission based on partial Mayo score at Week 52. Clinical remission based on partial Mayo score is defined as a partial Mayo score of ≤ 2 , and no individual subscore > 1 .

CD cohort

- Proportion of subjects with clinical remission at Week 12, defined as a CDAI score of ≤ 150 .
- Proportion of subjects with enhanced clinical response at Week 12, defined as a reduction of ≥ 100 points in CDAI score from baseline (Week 0).
- Proportion of subjects with corticosteroid-free remission, defined as subjects using oral corticosteroids at baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52.

Safety:

Safety measurements of vedolizumab IV Q4W will be based on adverse events (AEs), including adverse events of special interest (such as serious infections including opportunistic infections such as PML, liver injury, malignancies, infusion-related or infusion site reactions or systemic reactions and hypersensitivity), serious adverse events (SAEs), vital signs, results of standard laboratory tests (clinical chemistry, hematology, coagulation, urinalysis).

Statistical Considerations:

All statistical analysis will be performed separately for UC and CD cohorts.

UC cohort

For the primary endpoint, which is the proportion of subjects with clinical response at Week 12, point estimate and the 2-sided 95% exact confidence interval (CI) using the Clopper-Pearson method will be calculated. Missing data for the primary endpoint will be imputed using non-responder imputation method. An IA will be performed when the first 30 subjects complete assessments at Week 12 or ET. Based on the number of responders for the primary endpoint at IA, the decision (efficacy stopping, futility stopping or enrollment continuation) using statistical testing will be made. In the case of enrollment continuation, the sample size may be re-estimated. Statistical testing at final analysis (FA) for the primary endpoint will be performed once all subjects complete assessments at Week 12 or ET. The UC cohort may be completed with only between 31 and 59 subjects; in this case the FA will be performed. Stage 1 is defined as the period between the enrollment of the first subject and the completion of assessments at Week 12 or ET of the 30th subject, and stage 2 (if applicable) is defined as the period between the enrollment of the 31st subject and the completion of assessments at Week 12 or ET of the last enrolled subject in the re-estimated sample size. The IA will be performed using subjects enrolled in stage 1. The FA for the primary endpoint will be performed using subjects enrolled in stage 1 and stage 2 (if applicable). The re-estimated sample sizes and the corresponding criteria for statistical significance are determined according to the conditional error function by Englert and Kieser, 2012; and the promising zone approach by Mehta and Pocock, 2011. The statistical testing at FA will be conducted based on number of responders in both stages ($k_1 + k_2$) and the criteria to conclude statistical significance in the below tables, as applicable given the final sample size.

Decisions at IA

Number of responders at IA (k_1)	Decision
$k_1 \leq 7$	Futility stopping

$8 \leq k_1 \leq 12$	Enrollment continuation
$13 \leq k_1 \leq 30$	Efficacy stopping (statistical significance)

Re-estimated Sample Size and Criteria to Conclude Statistical Significance at FA for the Primary Endpoint

Number of responders at IA (k_1)	Re-estimated sample size (sample size in stage 2)	Criteria to conclude statistical significance at FA*
8	135 (105)	$k_1+k_2 > 37$ ($k_2 > 29$)
9	88 (58)	$k_1+k_2 > 25$ ($k_2 > 16$)
10	60 (30)	$k_1+k_2 > 18$ ($k_2 > 8$)
11	60 (30)	$k_1+k_2 > 18$ ($k_2 > 7$)
12	60 (30)	$k_1+k_2 > 18$ ($k_2 > 6$)

k_2 : Number of responders in stage 2

k_1+k_2 : Number of responders at FA for the primary endpoint

* $\alpha=0.025$ (one-sided) is kept using those criteria.

Re-estimated Sample Size and Criteria to Conclude Statistical Significance at FA for the Primary Endpoint ($N \geq 31$)

Re-estimated Sample Size (Sample Size in Stage 2)	Criteria to Conclude Statistical Significance at FA*
31-36 (1-6)	$k_1+k_2 > 13$
37-41 (7-11)	$k_1+k_2 > 14$
42-45 (12-15)	$k_1+k_2 > 15$
46-50 (16-20)	$k_1+k_2 > 16$
51-55 (21-25)	$k_1+k_2 > 17$
56-59 (26-29)	$k_1+k_2 > 18$

k_1 : Number of responders in stage 1

k_2 : Number of responders in stage 2

k_1+k_2 : Number of responders at FA for the primary endpoint

* $\alpha=0.025$ (one-sided) is kept using those criteria.

If the criterion for futility stopping is met, the study will be terminated for the UC cohort only (i.e., the study will continue for CD cohort).

If additional subjects are enrolled over the re-estimated sample size, those subjects will not be included in the statistical test for the FA. The point estimate of the response rate using all subjects will be provided descriptively as a secondary analysis for primary endpoint.

The primary endpoint will be listed.

CD cohort

For the primary endpoint, which is the proportion of subjects with clinical response at Week 12, point estimate and the 2-sided 95% exact CI will be calculated. Missing data for the primary endpoint will be imputed using non-responder imputation method.

The primary endpoint will be listed.

For both UC and CD cohorts, the secondary endpoints will be summarized descriptively and will be listed.

Sample Size Justification:

UC cohort

The statistical objective for the efficacy in UC cohort is to demonstrate that the proportion of subjects with clinical response at Week 12 based on modified Mayo score is statistically significantly greater than the threshold of 20%.

A study with 60 subjects will provide at least 90% power compared to the threshold rate of 20% using binomial test, assuming the true proportion of subjects with clinical response at Week 12 of 40%. An IA will be performed when the first 30 subjects complete assessments at Week 12 or ET. The decision of efficacy stopping, futility stopping or enrollment continuation will be made based on the statistical testing for the primary endpoint at IA. Sample size re-estimation will be also performed in the case of enrollment continuation. The UC cohort may be completed with any number of subjects greater than or equal to 31 subjects and then the FA will be performed.

CD cohort

The statistical objective for the efficacy in CD cohort is to achieve that the point estimate of the proportion of subjects with clinical response at Week 12 is greater than the threshold of 20% with a certain degree of precision.

A study with 23 subjects will provide at least 90% probability by binomial distribution to observe the point estimate of the proportion of subjects with clinical response at Week 12 $>20\%$ and will provide 2-sided 95% CI of approximately $\pm 20\%$ assuming the point estimate of 40% based on normal approximation. The CD cohort may be completed with any number of subjects greater than or equal to 15 subjects and then the FA will be performed. For example, a study with 15 subjects will also provide at least 90% probability to observe the point estimate of the proportion $>20\%$ and will provide two-sided 95% CI of approximately $\pm 25\%$.

3.0 LIST OF ABBREVIATIONS

5-ASA	5-aminosalicylate
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AVA	anti-vedolizumab antibody
BMI	body mass index
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRC	Central Reading Committee
CI	confidence interval
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
ECG	electrocardiogram
(e)CRF	(electronic) case report form
ET	Early Termination
EU	European Union
FA	final analysis
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GALT	gut-associated lymphoid tissue
GCP	Good Clinical Practice
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBI	Harvey-Bradshaw Index
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCP	healthcare provider
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IA	interim analysis
IAC	Independent Adjudication Committee
IBD	inflammatory bowel disease
IBDQ	inflammatory bowel disease questionnaire
ICH	International Council for Harmonisation
ID	identification
INR	international normalized ratio

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IRB	institutional review board
IV	intravenous(ly)
IWRS	interactive web response system
LFT	liver function test
LRG	leucine-rich α -2 glycoprotein
LTFU	long-term follow-up
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
NSAID	nonsteroidal anti-inflammatory drug
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PPS	per protocol set
PRO	patient-reported outcome
PTE	pretreatment event
Q4W	every 4 week(s)
Q8W	every 8 week(s)
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2 RT-PCR	severe acute respiratory syndrome-associated coronavirus 2 reverse transcription-polymerase chain reaction
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
UC	ulcerative colitis
USA	United States of America
ULN	upper limit of normal
WBC	white blood cell

3.1 Study Definitions

Terms	Definitions
Corticosteroid-free remission	Subjects using oral corticosteroids at baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52
Rescue therapy	<p>Any new medication or treatment, any increase in dose of a baseline medication, or any major surgical intervention required to treat new or unresolved symptoms for UC or CD (whichever is applicable for the subject), except for the following.</p> <ul style="list-style-type: none">• Initiation of medications or treatments or increase in dose of medications listed in Section 7.3.2• An increase in corticosteroid dose back to the Week 0 dose for subjects undergoing corticosteroid tapering within the guidelines presented in Section 7.3.3• Abscess drainage or the Seton method for anal lesions
<u>UC cohort</u>	
Clinical remission based on complete Mayo score	A complete Mayo score of ≤ 2 points and no individual subscore > 1 point.
Clinical remission based on modified Mayo score	A modified Mayo score of ≤ 2 points and no individual subscore > 1 point.
Clinical remission based on partial Mayo score	A partial Mayo score of ≤ 2 points and no individual subscore > 1 point.
Clinical response based on complete Mayo score	A reduction of ≥ 3 points and $\geq 30\%$ in complete Mayo score, and a decrease of ≥ 1 point in rectal bleeding subscore or a rectal bleeding subscore of ≤ 1 point from baseline (Week 0).
Clinical response based on modified Mayo score	A reduction of ≥ 2 points and $\geq 25\%$ in modified Mayo score, and a decrease of ≥ 1 point in rectal bleeding subscore or a rectal bleeding subscore of ≤ 1 point from baseline (Week 0).
Disease worsening	<p>Disease worsening is defined as meeting at least one of the below criteria.</p> <ul style="list-style-type: none">• An increase in partial Mayo score ≥ 3 points from the Week 12 value on <u>1 visit</u> (or an increase to 9 points on <u>1 visit</u> if the Week 12 value > 6) and a partial Mayo score of ≥ 5 points. The investigator must be certain that the increase in partial Mayo score is attributed to UC only. If the increase in partial Mayo score is not considered to be related to UC, the subject can continue this study.• An increase in partial Mayo score ≥ 3 points from the Week 12 value on <u>2 consecutive visits</u> (or an increase to 9 points on <u>2 consecutive visits</u> if the Week 12 value > 6) and a partial Mayo score of ≥ 5 points.
Mucosal healing	A Mayo endoscopic subscore of ≤ 1 point.
<u>CD cohort</u>	
Clinical remission	A Crohn's Disease Activity Index (CDAI) score ≤ 150 points.
Clinical response	A reduction of ≥ 70 points in CDAI score from baseline (Week 0).
Disease worsening	<p>Disease worsening is defined as meeting at least one of the below criteria.</p> <ul style="list-style-type: none">• An increase in CDAI score of ≥ 100 points from the Week 12 value on <u>1 visit</u> and a CDAI score of ≥ 220 points. The investigator must be certain that the increase in CDAI is attributed to CD only. If the increase in CDAI is not considered to be related to CD, the subject can continue this study.• An increase in CDAI score of ≥ 100 points from the Week 12 value on <u>2 consecutive visits</u> and a CDAI score of ≥ 220 points.
Enhanced clinical response	A reduction of ≥ 100 points in CDAI score from baseline (Week 0).

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4.0 INTRODUCTION

4.1 Background

Inflammatory Bowel Disease (IBD) is a chronic, relapsing, remitting inflammatory condition of unknown etiology that affects the gastrointestinal (GI) tract. IBD mainly consists of 2 diseases, ulcerative colitis (UC) and Crohn's disease (CD).

UC is characterized by a superficial inflammation of the mucosa that begins from the rectum and extends proximally. The number of patients with UC in Japan has increased over the past decades, with the latest estimate exceeding 160,000 [1]. Clinical manifestations include diarrhea, typically bloody, as well as abdominal pain, fecal urgency and incontinence.

CD is characterized by an inflammation that may involve any portion of the GI tract in a transmural manner. The number of patients with CD in Japan has increased over the past decades, with the latest estimate exceeding 40,000 [2]. Clinical manifestations include diarrhea, abdominal pain, fecal urgency and incontinence.

In IBD, systemic symptoms such as fever, weight loss, malaise and fatigue are indicators of a more severe disease. Both diseases may be complicated by extraintestinal manifestations. Current treatment options for IBD that are recommended in the Japanese guidelines include 5-aminosalicylates, corticosteroids, immunomodulators and biologics [3], which are effective but are not curative.

Vedolizumab (also known as MLN0002) is a recombinant humanized monoclonal antibody composed of 2 light chains of the κ subclass and 2 immunoglobulin (Ig) G1 heavy chains. Vedolizumab binds specifically to the human lymphocyte integrin $\alpha 4\beta 7$. The $\alpha 4\beta 7$ integrin mediates lymphocyte trafficking to GI mucosa and gut-associated lymphoid tissue (GALT) 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 [4-7]. As a result, vedolizumab impairs the migration of gut-homing leukocytes into GI mucosa [8] and acts as a gut-selective immunomodulator.

Vedolizumab intravenous (IV) has been granted marketing approval in several regions, including the United States of America (USA), European Union (EU), and Japan. Vedolizumab IV is approved for the treatment and maintenance therapy of adult patients with moderately to severely active UC and CD, who have failed conventional treatment, such as corticosteroids, immunomodulators or biologics. The approved dosing and administration regimen in Japan is 300 mg of vedolizumab infused intravenously at Weeks 0, 2 and 6, then once every 8 weeks (Q8W) thereafter, with no increase in dosing frequency [9].

4.1.1 Clinical Experience with Vedolizumab IV Every 4 Week Dosing

Vedolizumab IV every 4 week (Q4W) dosing was administered during the maintenance phase of international phase 3 studies in subjects with UC (Study C13006) and CD (Study C13007), and in an international long-term extension study in subjects with UC or CD (Study C13008) [10-14].

In both Studies C13006 and C13007, a superiority of vedolizumab IV Q4W to placebo was demonstrated during the maintenance phase in subjects who achieved clinical response in the induction phase, and a similar efficacy was observed between the Q4W and Q8W arms. Clinical remission rates and clinical response rates increased in the subgroup of subjects who received vedolizumab IV Q4W in Study C13008 after prematurely discontinuing Study C13006 or Study C13007 due to lack of efficacy with vedolizumab IV Q8W dosing. In addition, no significant safety concerns following administration of vedolizumab IV Q4W were noted in any of these studies.

The efficacy and safety of vedolizumab IV Q4W in each study are summarized below.

4.1.1.1 Study C13006

Study C13006 was an international, phase 3, randomized, placebo-controlled, double-blind study to evaluate the efficacy and safety when vedolizumab 300 mg IV was administered at 0, 2, and 6 weeks and at Q8W or Q4W dosing thereafter in subjects with moderate to severe UC. This study consisted of an induction phase (Week 0 to 6) and a maintenance phase (Week 6 to 52). Only subjects who had received induction treatment with vedolizumab IV and had achieved clinical response at Week 6 were randomized into the maintenance phase. Subjects eligible for the maintenance phase were randomized in a 1:1:1 ratio to placebo, vedolizumab IV Q8W or vedolizumab IV Q4W.

The primary endpoint for the maintenance phase, clinical remission rates at Week 52, were 15.9%, 41.8%, and 44.8% for placebo, Q8W and Q4W, respectively. Differences from placebo were 26.1% (95% CI: 14.9, 37.2) for Q8W arm and 29.1% (95% CI: 17.9, 40.4) for Q4W arm. Clinical remission rates of Q8W and Q4W arms were significantly higher than placebo ($p < 0.0001$ for both). When comparing Q8W and Q4W arms, a secondary endpoint, corticosteroid-free remission rates at Week 52 for Q4W arm (45.2%) was higher than Q8W arm (31.4%), however there were no major differences between Q8W and Q4W arms in the primary endpoint and the other secondary endpoints [10].

Vedolizumab IV was well tolerated in the induction and maintenance phases. The safety profiles were similar between Q8W and Q4W arms [10].

4.1.1.2 Study C13007

Study C13007 was an international, phase 3, randomized, placebo-controlled, double-blind study to evaluate the efficacy and safety when vedolizumab 300 mg IV was administered at 0, 2, and 6 weeks and at Q8W or Q4W dosing thereafter in subjects with moderate to severe CD. The study design was similar to that of Study C13006.

The primary endpoint for the maintenance phase, clinical remission rates at Week 52, were 21.6%, 39.0%, and 36.4% for placebo, Q8W arm and Q4W arm, respectively. Differences from placebo were 17.4% (95% CI: 7.3, 27.5) for Q8W and 14.7% (95% CI: 4.6, 24.7) for Q4W arm. Clinical remission rates of both Q8W and Q4W arms were significantly higher than placebo ($p = 0.0007$, $p = 0.0042$, respectively). When comparing Q8W and Q4W arms, there were no

major differences in the primary endpoint and any of the secondary endpoints for the maintenance phase [11].

Vedolizumab IV was well tolerated in the induction and maintenance phases. The safety profiles were similar between Q8W and Q4W arms [11].

4.1.1.3 Study C13008

Study C13008 was an international long-term study in subjects who completed the preceding study involving subjects with UC or CD (Study C13004, C13006, C13007 or C13011), subjects who prematurely discontinued Study C13006 or C13007, and patients with UC or CD who have never received vedolizumab IV (new subjects) to evaluate the safety and efficacy of open-label vedolizumab IV Q4W. In Study C13008, the disease activity of UC or CD in long-term administration of vedolizumab IV was evaluated based on changes in partial Mayo score and Harvey-Bradshaw Index (HBI) from baseline, respectively, as an exploratory endpoint.

As a post-hoc analysis, changes in clinical response rates and clinical remission rates over time in subjects who received vedolizumab IV Q4W in Study C13008 after prematurely discontinuing Study C13006 or Study C13007 (the preceding study) due to lack of efficacy in the vedolizumab IV Q8W group were evaluated. Of the 32 UC subjects who met such criterion, 19% (n = 6/32) and 6% (n = 2/32) had clinical response and remission, respectively, at enrollment into Study C13008. After 28 weeks of vedolizumab IV Q4W dosing in these 32 UC subjects, clinical response and remission were achieved by 53% (n = 17/32) and 25% (n = 8/32), respectively [12]. Of the 57 CD subjects who met such criterion, 39% (n = 22/57) and 4% (n = 2/57) had clinical response and remission, respectively, at enrollment into Study C13008. After 28 weeks of vedolizumab IV Q4W dosing in these 57 CD subjects, clinical response and remission were achieved by 54% (n = 31/57) and 23% (n = 13/57), respectively [13].

Another post-hoc analysis was performed to investigate the efficacy of vedolizumab IV Q4W in C13008 for UC subjects who discontinued vedolizumab IV Q8W maintenance treatment in C13006 due to lack of efficacy. For subjects with a partial Mayo score of ≥ 4 (n=26) at baseline of C13008, clinical response rates based on partial Mayo score were 38.5%, 50.0%, 42.3%, and 34.6% at Weeks 4, 8, 12, and 20, respectively. For subjects with a partial Mayo score of ≥ 5 (n=21) at baseline of C13008, clinical response rates based on partial Mayo score were 47.6%, 61.9%, 52.4%, and 42.9% at Weeks 4, 8, 12, and 20, respectively.

Similarly, a post-hoc analysis was performed for CD subjects who discontinued vedolizumab IV Q8W maintenance treatment in C13007 due to lack of efficacy. For those subjects, clinical response rates based on HBI score (as defined by a decrease of ≥ 3 points in HBI score) were 57.9%, 52.6%, 54.4%, and 50.9% at Weeks 4, 8, 12, and 20, respectively. Clinical remission rates based on HBI score (as defined by HBI score of ≤ 4) were 21.1%, 33.3%, 35.1%, and 36.8% at Weeks 4, 8, 12, and 20, respectively.

Long-term administration of vedolizumab IV Q4W was well tolerated in Study C13008 without significant safety concerns [14].

4.2 Rationale for the Proposed Study

Although vedolizumab IV has shown its efficacy as a maintenance therapy for both UC [10, 15] and CD [11, 16], secondary loss of response to maintenance therapy with vedolizumab IV Q8W dosing has been observed in both clinical trials and clinical practice [12, 13, 17-18]. For some patients with secondary loss of response, a regained response can be achieved with a more frequent dosing of vedolizumab IV [12, 13, 17-19]. Though vedolizumab IV Q4W dosing has been approved in the EU, such option is currently unavailable in Japan.

Hence, this phase 3 study has been designed to evaluate the efficacy, safety and pharmacokinetics (PK) of vedolizumab IV Q4W in Japanese patients with moderate to severe UC or CD who have lost response during the maintenance therapy with vedolizumab IV Q8W. The Q4W dosing regimen was selected based on previously evaluated phase 3 clinical trials of vedolizumab IV (C13006, C13007 and C13008).

4.3 Benefit/Risk Profile

The proposed study is designed to evaluate the efficacy, safety, and pharmacokinetics of vedolizumab IV Q4W in Japanese patients with moderate to severe UC or CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.

As previously stated in Section 4.1.1, the safety profile of vedolizumab IV Q4W dosing in subjects with UC and CD has been confirmed in international phase 3 studies [10, 11], with no unexpected or new safety signals in the long-term study [14]. Vedolizumab IV Q4W has a similar safety profile to Q8W, and is approved in the EU based on these results.

On the other hand, international data from clinical trials and clinical practice have shown favorable results with Q4W dosing [12, 13, 17-19].

Therefore, the risk profile of vedolizumab IV Q4W is in line with the approved dosing regimen (Q8W) and there is a suggestion of benefit from international studies. This study is designed to further characterize the risk benefit of dose escalating to Q4W.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To assess the effect of vedolizumab IV Q4W on clinical response at Week 12 in Japanese subjects with moderate to severe UC or CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.

5.1.2 Secondary Objectives

- To assess the safety of vedolizumab IV Q4W in Japanese subjects with moderate to severe UC or CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.

UC cohort

- To assess the effect of vedolizumab IV Q4W on clinical remission based on modified Mayo score at Week 12 in Japanese subjects with moderate to severe UC who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.
- To assess the effect of vedolizumab IV Q4W on mucosal healing based on Mayo endoscopic subscore at Week 12 in Japanese subjects with moderate to severe UC who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.
- To assess the effect of vedolizumab IV Q4W on corticosteroid-free remission based on partial Mayo score at Week 52 in Japanese subjects with moderate to severe UC who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W and achieved clinical response at Week 12.

CD cohort

- To assess the effect of vedolizumab IV Q4W on clinical remission based on Crohn's Disease Activity Index (CDAI) at Week 12 in Japanese subjects with moderate to severe CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.
- To assess the effect of vedolizumab IV Q4W on enhanced clinical response based on CDAI at Week 12 in Japanese subjects with moderate to severe CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.
- To assess the effect of vedolizumab IV Q4W on corticosteroid-free remission based on CDAI at Week 52 in Japanese subjects with moderate to severe CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W and achieved clinical response at Week 12.

5.1.3 Exploratory/Additional Objectives

- To assess the pharmacokinetics of vedolizumab IV Q4W in Japanese subjects with moderate to severe UC or CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.
- To assess the immunogenicity of vedolizumab IV Q4W in Japanese subjects with moderate to severe UC or CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.
- To assess the effect of vedolizumab IV Q4W on fecal calprotectin at Week 12 in Japanese subjects with moderate to severe UC or CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.
- To assess the effect of vedolizumab IV Q4W on changes in leucine-rich α -2 glycoprotein (LRG) at Weeks 4, 8 and 12 in Japanese subjects with moderate to severe UC or CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.
- To assess the effect of vedolizumab IV Q4W on patient-reported outcomes (PRO) at Week 12 in Japanese subjects with moderate to severe UC or CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.

UC cohort

- To assess the effect of vedolizumab IV Q4W on changes in modified Mayo score at Week 12 from baseline in Japanese subjects with moderate to severe UC who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.
- To assess the effect of vedolizumab IV Q4W on clinical response and clinical remission based on complete Mayo score at Week 12 in Japanese subjects with moderate to severe UC who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.
- To assess the effect of vedolizumab IV Q4W on changes in partial Mayo scores and its subscores from baseline to Week 52 in Japanese subjects with moderate to severe UC who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.

CD cohort

- To assess the effect of vedolizumab IV Q4W on changes in C-reactive protein (CRP) levels from baseline to Week 52 in Japanese subjects with moderate to severe CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.

- To assess the effect of vedolizumab IV Q4W on CDAI and its subscores from baseline to Week 52 in Japanese subjects with moderate to severe CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W.

5.2 Endpoints

5.2.1 Primary Endpoints

UC cohort

- Proportion of subjects with clinical response at Week 12 based on modified Mayo score, defined as a reduction of ≥ 2 points and $\geq 25\%$ in modified Mayo score, and a decrease of ≥ 1 point in rectal bleeding subscore or rectal bleeding subscore of ≤ 1 from baseline (Week 0).

CD cohort

- Proportion of subjects with clinical response at Week 12, defined as a reduction of ≥ 70 points in CDAI score from baseline (Week 0).

5.2.2 Secondary Endpoints

UC cohort

- Proportion of subjects with clinical remission at Week 12 based on modified Mayo score, defined as a modified Mayo score of ≤ 2 , and no individual subscore > 1 .
- Proportion of subjects with mucosal healing at Week 12, defined as a Mayo endoscopic subscore of ≤ 1 , in subjects with baseline Mayo endoscopic subscore of ≥ 2 .
- Proportion of subjects with corticosteroid-free remission based on partial Mayo score, defined as subjects using oral corticosteroids at baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission based on partial Mayo score at Week 52. Clinical remission based on partial Mayo score is defined as a partial Mayo score of ≤ 2 , and no individual subscore > 1 .

CD cohort

- Proportion of subjects with clinical remission at Week 12, defined as a CDAI score of ≤ 150 .
- Proportion of subjects with enhanced clinical response at Week 12, defined as a reduction of ≥ 100 points in CDAI score from baseline (Week 0).
- Proportion of subjects with corticosteroid-free remission, defined as subjects using oral corticosteroids at baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52.

5.2.3 Exploratory/Additional Endpoints

UC cohort

- Change in modified Mayo score at Week 12 from baseline (Week 0).
- Proportion of subjects with clinical response at Week 12 based on complete Mayo score, defined as a reduction of ≥ 3 points and $\geq 30\%$ in complete Mayo score, and a decrease of ≥ 1 point in rectal bleeding subscore or rectal bleeding subscore of ≤ 1 from baseline (Week 0).
- Proportion of subjects with clinical remission at Week 12 based on complete Mayo score, defined as a complete Mayo score of ≤ 2 , and no individual subscore > 1 .
- Changes in partial Mayo score at Weeks 4, 8, 12, and until Week 52 from baseline (Week 0).
- Changes in Mayo subscores at Weeks 4, 8, 12, and until Week 52 from baseline (Week 0).
- Changes in fecal calprotectin at Week 12 from baseline (screening).
- Changes in LRG at Weeks 4, 8, and 12 from baseline (Week 0).
- Changes in Inflammatory Bowel Disease Questionnaire (IBDQ) score at Week 12 from baseline (Week 0).

CD cohort

- Change in CRP levels at Weeks 4, 8, 12, and until Week 52 from baseline (Week 0).
- Changes in CDAI score at Weeks 4, 8, 12, and until Week 52 from baseline (Week 0).
- Changes in CDAI subscores at Weeks 4, 8, 12, and until Week 52 from baseline (Week 0).
- Changes in fecal calprotectin at Week 12 from baseline (screening).
- Changes in LRG at Weeks 4, 8, and 12 from baseline (Week 0).
- Changes in IBDQ score at Week 12 from baseline (Week 0).

5.2.4 Pharmacokinetic Endpoints

- Trough serum concentration of vedolizumab.

5.2.5 Immunogenicity Endpoints

- Proportion of subjects with positive anti-vedolizumab antibody (AVA) and neutralizing AVA during the study.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 3, multicenter, open-label, single-arm study to evaluate the efficacy, safety, and pharmacokinetics of vedolizumab IV Q4W in Japanese subjects with moderate to severe UC or CD, who experienced secondary loss of response during maintenance therapy with commercially available vedolizumab IV Q8W. This study consists of screening, treatment, and extension phases.

The screening phase will involve screening tests of consenting subjects who visit a study site between 28 and 3 days before the start of treatment (i.e., vedolizumab IV Q4W). Subjects meeting the eligibility criteria based on the inclusion and exclusion criteria on the first day of treatment (Day 1) will be enrolled into the treatment phase. The interval between the last dose of commercially available vedolizumab IV and Day 1 must be within the range of 4 to 8 weeks.

Subjects enrolled into the treatment phase will receive vedolizumab 300 mg IV at Weeks 0, 4, and 8 in an unblinded manner. The primary efficacy evaluation will be performed at Week 12.

Subjects showing a clinical response* at Week 12 can enter into the extension phase and can continue to receive vedolizumab IV starting from Week 12 and then every 4 weeks in an unblinded manner, until the date of marketing approval of vedolizumab IV Q4W, study termination, or subject withdrawal. Subjects not showing a clinical response at Week 12 will discontinue the study at Week 12 (considered as Week 12 completers with non-response).

* Clinical response is defined for UC and CD, respectively, as follows;

- For UC, a reduction of ≥ 2 points and $\geq 25\%$ from baseline in modified Mayo score (0-9; composed of stool frequency [0-3], rectal bleeding [0-3], and endoscopic [0-3] subscores), and a decrease of ≥ 1 point in rectal bleeding subscore or rectal bleeding subscore of ≤ 1 .
- For CD, a reduction of ≥ 70 points from baseline in CDAI score.

The end-of-study examination will be performed at 16 weeks after the last dose in subjects who received the study drug. Safety evaluation will be performed throughout the study period. Blood samples for pharmacokinetic evaluation will be collected at Weeks 0, 4, 8, 12, and Week 52 or Early Termination (ET) (prior to Week 52). Blood samples for the AVA and neutralizing AVA test will be collected at Weeks 0, 4, 8, 12, Week 52 or ET (prior to Week 52), Final Safety Follow-up Visit, and at Unscheduled Visit triggered by suspected immunologically related adverse events.

Endoscopy will be performed in the rectum and sigmoid colon at screening and at Week 12 or ET for the UC cohort. All endoscopies will be centrally read. Inclusion into the treatment phase (at Week 0) will be decided based on the central reader's assessment, while enrollment into the extension phase (at Week 12) will be decided based on the investigator's assessment. Efficacy analyses will be performed using Mayo endoscopic subscore assessed by the central reader. Endoscopy will not be performed for the CD cohort.

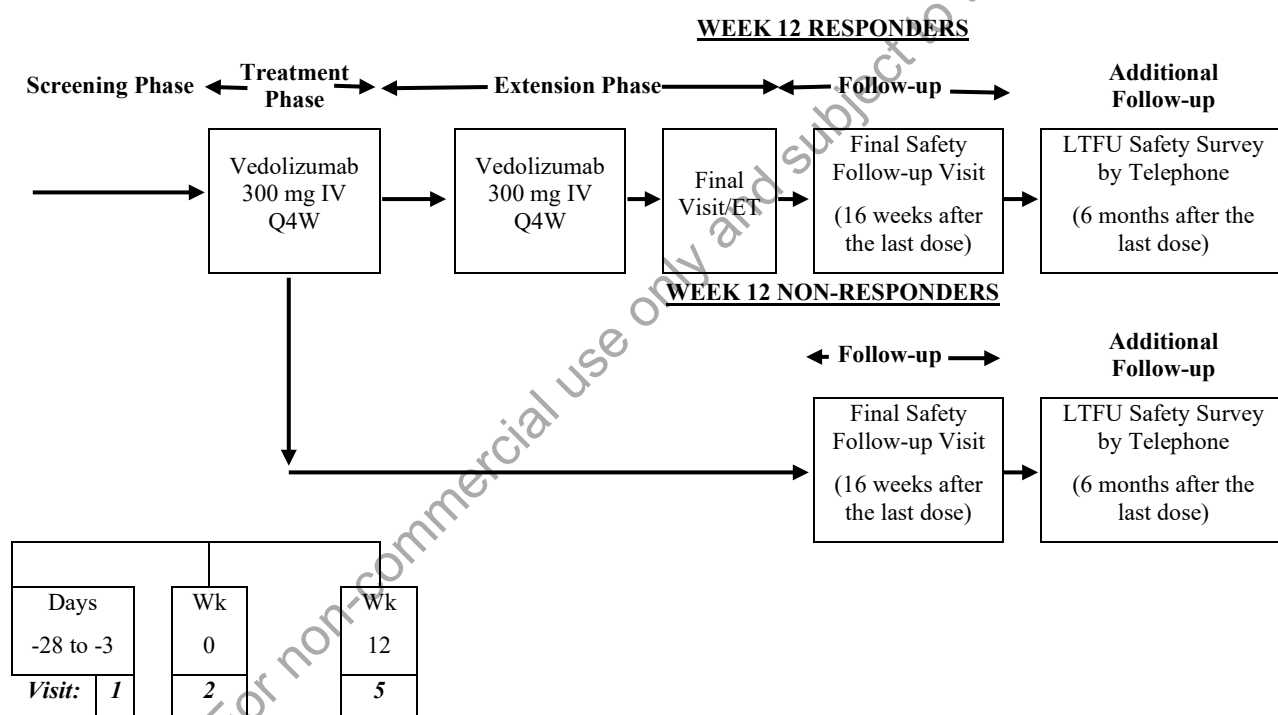
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Additionally, the follow-up safety-survey by telephone is to be performed 6 months after the last dose of study drug.

For the UC cohort, an interim analysis (IA) will be performed when the first 30 subjects complete assessments at Week 12 or ET. Based on the outcome of IA, a decision will be made on either of efficacy stopping, futility stopping, or study continuation with sample size re-estimation.

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



IV = Intravenous, ET = Early termination, LTFU = Long-term follow-up, Q4W = Every 4 weeks, Wk = Week,

6.2 Justification for Study Design, Dose, and Endpoints

The study population is defined as “Japanese patients with moderate to severe UC or CD who experienced secondary loss of response during maintenance therapy with vedolizumab IV Q8W in clinical practice” in order to evaluate the efficacy, safety, and pharmacokinetics of vedolizumab IV Q4W. The following inclusion criterion was set to define the subjects for this study.

- The subject has moderate to severe UC or CD, who had previously shown clinical response in initial treatment with commercially available vedolizumab IV, then experienced secondary loss of response during maintenance therapy with commercially available vedolizumab IV Q8W (refer to Section 7.1 for details of previous clinical response and secondary loss of response).

The clinical course of each patient from the start of initial treatment with commercially available vedolizumab IV, transfer to maintenance therapy, to secondary loss of response will be confirmed by referring to medical records used in clinical practice to enroll patients who meet the inclusion criteria in this study. However, it is expected that in routine clinical practice, assessments with Mayo score for UC and CDAI for CD may not necessarily be available at the start of initial treatment or at the time of transfer to maintenance therapy. To compensate for the difficulty to make the decision of previous “clinical response” and “secondary loss of response” based on stringent criteria for all subjects, multiple definitions for each term are set so that investigators may refer to them and decide as objectively as possible.

Furthermore, additional criteria were set to ensure that the disease is in its active state at the start of this study (refer to Section 7.1 for details).

The number of patients with UC or CD who experience secondary loss of response to vedolizumab IV Q8W are estimated to be insufficient to conduct the study in a randomized, double-blind design from a feasibility point of view. Thus, an open-label, single-arm design has been chosen for the current study due to limited number of subject enrollment expected in both UC and CD cohorts.

The vedolizumab 300 mg IV Q4W dosing regimen was selected based on previously evaluated international phase 3 clinical trials of vedolizumab 300 mg IV (C13006, C13007, and C13008) [10-14].

The primary and secondary endpoints in this study are the same as those in the previous clinical studies with vedolizumab IV in UC subjects (induction phases of Study C13006 and Study CCT-101 [10, 15]) or CD subjects (induction phases of Study C13007 and Study CCT-001 [11, 16]), except for changes in definitions of endpoints to adapt modified Mayo score for UC and the timepoint.

Modified Mayo score (0-9; composed of stool frequency [0-3], rectal bleeding [0-3], and endoscopic [0-3] subscores) will be used for the primary and secondary endpoints for UC to exclude more subjective component of Mayo score (i.e., physician’s global assessment subscore), in order to evaluate the efficacy of vedolizumab IV Q4W in this open-label study without a control group.

For both UC and CD cohorts, the time point for primary efficacy evaluation (Week 12) was determined based on a post-hoc analysis reference data from C13008 (refer to Section 4.1.1.3 for details) and the estimate that the trough serum concentration of vedolizumab IV after dose intensification from Q8W to Q4W will increase through Weeks 4, 8, and 12, and will reach steady state Week 12, based on the half-life of vedolizumab IV which is around 25 days.

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 risk/benefit profile for vedolizumab, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Study-specific criteria for terminating the study (e.g., study meets predefined rule for futility or benefit).

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 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 prior to first dose.

7.1 Inclusion Criteria

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

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is Japanese male or female, aged 18 to 80 years, inclusive.
4. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use barrier method of contraception (e.g., condom with or without spermicide) from signing of informed consent throughout the duration of the study and for 6 months after last dose.
5. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use a highly effective method of contraception* from signing of informed consent throughout the duration of the study and for 6 months after the last dose.

*Definitions and highly effective methods of contraception are defined in Section 9.1.10 and reporting responsibilities are defined in Section 9.1.11.

UC cohort

1. The subject has a diagnosis of UC established at least 6 months prior to screening based on the "Diagnostic criteria for UC (January 2020 revision)" as outlined in "Ulcerative colitis and Crohn's disease: diagnostic criteria and treatment guidelines (March 2020 revision)" issued by "Research Group for Intractable Inflammatory Bowel Disease" which is conducted as part of "Health Labor and Welfare Science Research Grants Subsidy Policy Research Project for Intractable Diseases." [3]
2. The subject has moderate to severe UC, who had previously shown clinical response* in initial treatment with commercially available vedolizumab IV, then experienced secondary loss of response** during maintenance therapy with commercially available vedolizumab IV Q8W.

*Previous "clinical response" is to be judged by the investigators referring to one of the following criteria.

- Reduction of ≥ 2 points and $\geq 25\%$ in modified Mayo score, and a decrease of ≥ 1 point in rectal bleeding subscore or rectal bleeding subscore of ≤ 1 , from the start of initial treatment with commercially available vedolizumab IV.

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- Reduction of ≥ 2 points and $\geq 25\%$ in partial Mayo score, and a decrease of ≥ 1 point in rectal bleeding subscore or rectal bleeding subscore of ≤ 1 , from the start of initial treatment with commercially available vedolizumab IV.
- Significant improvement on endoscopy (i.e., a decrease of ≥ 2 points in Mayo endoscopic subscore).

** “Secondary loss of response” is to be judged by the investigators referring to one of the following criteria.

- Increase of ≥ 2 points in modified Mayo score, and an increase of ≥ 1 point in rectal bleeding subscore or rectal bleeding subscore ≥ 2 , from the start of maintenance therapy with commercially available vedolizumab IV.
 - Increase of ≥ 2 points in partial Mayo score, and an increase of ≥ 1 point in rectal bleeding subscore or rectal bleeding subscore ≥ 2 , from the start of maintenance therapy with commercially available vedolizumab IV.
 - Significant deterioration on endoscopy (i.e., an increase of ≥ 2 points in Mayo endoscopic subscore).
3. The subject has active UC as determined by a modified Mayo score of ≥ 5 at baseline (within 10 days prior to the start of treatment phase), with a Mayo rectal bleeding subscore of ≥ 1 at baseline (within 10 days prior to the start of treatment phase) and a Mayo endoscopic subscore of ≥ 1 as assessed by the central reader.
 4. Subjects with extensive colitis or pancolitis of >8 years duration or left-sided colitis >12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of the initial screening visit (if not performed in previous 12 months, must be performed prior to or during the screening phase).
 5. Subjects with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factors must be up-to-date on colorectal cancer surveillance (may be performed during the screening phase).

CD cohort

1. The subject has a diagnosis of CD established at least 6 months prior to screening based on the “Diagnostic criteria for CD (January 2020 revision)” as outlined in “Ulcerative colitis and Crohn’s disease: diagnostic criteria and treatment guidelines (March 2020 revision)” issued by “Research Group for Intractable Inflammatory Bowel Disease” which is conducted as part of “Health Labor and Welfare Science Research Grants Subsidy Policy Research Project for Intractable Diseases.” [3]
2. The subject has moderate to severe CD, who had previously shown clinical response* in initial treatment with commercially available vedolizumab IV, then experienced secondary loss of response** during maintenance therapy with commercially available vedolizumab IV Q8W.

*Previous “clinical response” is to be judged by the investigators referring to one of the following criteria.

- Reduction of ≥ 70 points in CDAI score from the start of initial treatment with commercially available vedolizumab IV.
- Reduction of ≥ 3 points in HBI score from the start of initial treatment with commercially available vedolizumab IV.

** “Secondary loss of response” is to be judged by the investigators referring to one of the following criteria.

- Increase of ≥ 70 points in CDAI score from the start of maintenance therapy with commercially available vedolizumab IV.
- Increase of ≥ 3 points in HBI score from the start of maintenance therapy with commercially available vedolizumab IV.

3. The subject has active CD as determined by a CDAI score of ≥ 220 at baseline (within 10 days prior to the start of treatment phase).
4. The subject has a CRP level > 3.0 mg/L during the screening phase.
5. The subject has CD involvement of the ileum and/or colon, at a minimum.
6. Subjects with extensive colitis or pancolitis of > 8 years duration or left-sided colitis > 12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of the initial screening visit (if not performed in previous 12 months, must be performed before the screening phase).
7. Subjects with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age > 50 years, or other known risk factors must be up-to-date on colorectal cancer surveillance.

7.2 Exclusion Criteria

The exclusion criteria are divided into 3 categories: GI, infectious disease, and general. Any subject who meets any of the following criteria listed in Sections 7.2.1 through 7.2.3 will not qualify for entry into the study.

7.2.1 Gastrointestinal Exclusion Criteria

UC cohort

1. The subject has evidence of abdominal abscess or toxic megacolon at screening.
2. The subject has had extensive colonic resection, subtotal or total colectomy.
3. The subject has had ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine.

4. The subject has received any of the investigational or approved non-biologic therapies (e.g., cyclosporine, tacrolimus or tofacitinib, except for those specifically listed in Section 7.3.1) for the treatment of underlying disease within 30 days or 5 half-lives of screening (whichever is longer).
5. The subject has received any investigational or approved biologic or biosimilar agent other than vedolizumab within 60 days or 5 half-lives of screening (whichever is longer).
6. The subject has used topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories within 2 weeks prior to the first dose of study drug.
7. The subject requires surgical intervention for UC at screening.
8. The subject has a history or evidence of adenomatous colonic polyps that have not been removed or has a history or evidence of colonic mucosal dysplasia.
9. The subject has a suspected or confirmed diagnosis of indeterminate colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, nonsteroidal anti-inflammatory drug (NSAID)-induced colitis, or microscopic colitis.
10. The subject has experienced one or more serious adverse events (SAEs) related to vedolizumab IV.
11. The subject's secondary loss of response could be explained, in the opinion of the investigator, by non-compliance to the treatment or missed doses of vedolizumab IV.

CD cohort

1. The subject has evidence of abdominal abscess at screening.
2. The subject has had extensive colonic resection, subtotal or total colectomy.
3. The subject has a history of >3 small bowel resections or diagnosis of short bowel syndrome.
4. The subject has received tube feeding, defined formula diets, or parenteral alimentation within 28 days prior to the first dose of study drug.
5. The subject has ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine.
6. The subject has received any of the investigational or approved non-biologic therapies (e.g., cyclosporine, tacrolimus or tofacitinib, except for those specifically listed in Section 7.3.1) for the treatment of underlying disease within 30 days or 5 half-lives of screening (whichever is longer).
7. The subject has received any investigational or approved biologic or biosimilar agent other than vedolizumab IV within 60 days or 5 half-lives of screening (whichever is longer).

8. The subject has used topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories within 2 weeks prior to the first dose of study drug.
9. The subject currently requires or is anticipated to require surgical intervention for CD during the study.
10. The subject has a history or evidence of adenomatous colonic polyps that have not been removed.
11. The subject has a history or evidence of colonic mucosal dysplasia.
12. The subject has a suspected or confirmed diagnosis of indeterminate colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, NSAID-induced colitis, or microscopic colitis.
13. The subject has experienced one or more SAEs related to vedolizumab IV.
14. The subject's secondary loss of response could be explained, in the opinion of the investigator, by non-compliance to the treatment or missed doses of vedolizumab IV.

7.2.2 Infectious Disease Exclusion Criteria

1. The subject has a clinically significant active infection (e.g., pneumonia, pyelonephritis or coronavirus disease 2019 [COVID-19]) within 30 days prior to screening or during screening, or has an ongoing chronic infection, or has lingering COVID-19-related symptoms, if previously infected with COVID-19.
2. The subject has evidence of, or treatment for, *C. difficile* infection or other intestinal pathogen within 28 days prior to the first dose of study drug.
3. The subject has chronic hepatitis B virus (HBV) infection* or chronic hepatitis C virus (HCV) infection (Note: If there is documented evidence that the subject had tested negative at the time of initiating treatment with or during treatment with vedolizumab IV, then the screening tests can be skipped).

*HBV immune subjects (i.e., being hepatitis B surface antigen [HBsAg]-negative and hepatitis B surface antibody [HBsAb]-positive) may, however, be included. Investigators should follow relevant guidelines and closely monitor subjects with positive hepatitis B core antibody (HBcAb) for any signs and symptoms of HBV activation.

4. The subject has active or latent tuberculosis (TB), as evidenced by either a positive T-SPOT TB test or a tuberculin skin test reaction ≥ 5 mm within 30 days prior to screening or during the screening phase (Note: If there is documented evidence that the subject had tested negative at the time of initiating treatment with or during treatment with vedolizumab IV, then the screening test can be skipped).
5. The subject has any identified congenital or acquired immunodeficiency (e.g., common variable immunodeficiency, human immunodeficiency virus (HIV) infection, organ transplantation) (Note: If there is documented evidence that the subject had tested

negative for HIV at the time of initiating treatment with or during treatment with vedolizumab IV, then the screening test can be skipped).

7.2.3 General Exclusion Criteria

1. The subject has known or suspected intolerance or hypersensitivity to vedolizumab or closely related compounds, or any of the vedolizumab IV excipients.
2. The subject has active cerebral/meningeal disease, or signs/symptoms of progressive multifocal leukoencephalopathy (PML) or any history of PML at screening.
3. The subject has any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise subject safety.
4. The subject has had any surgical procedure requiring general anesthesia within 30 days prior to screening or is planning to undergo major surgery during the study period.
5. The subject has any history of malignancy, except for the following: (a) adequately treated nonmetastatic basal cell skin cancer; (b) squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to screening; and (c) history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years prior to screening. Subjects with remote history of malignancy (e.g., >10 years since completion of curative therapy without recurrence) will be considered based on the nature of the malignancy and the therapy received and must be discussed with the sponsor on a case-by-case basis prior to screening.
6. The subject has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, demyelinating or neurodegenerative disease.
7. The subject has any of the following laboratory abnormalities during the screening phase:
 - i. Hemoglobin level <8 g/dL.
 - ii. White blood cell (WBC) count < $3 \times 10^9/L$.
 - iii. Lymphocyte count < $0.5 \times 10^9/L$.
 - iv. Platelet count < $100 \times 10^9/L$ or > $1200 \times 10^9/L$.
 - v. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > $3 \times$ the upper limit of normal (ULN).
 - vi. Alkaline phosphatase > $3 \times$ ULN.
 - vii. Serum creatinine > $2 \times$ ULN.
8. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to screening.

9. The subject has an active psychiatric problem that, in the investigator's opinion, may interfere with compliance with study procedures.
10. The subject or caregiver is unable to attend all the study visits or comply with study procedures.
11. The subject takes excluded medications listed in Section 7.3.
12. Female subjects who are lactating or have a positive serum pregnancy test during the screening phase or a positive urine pregnancy test at Week 0, prior to study drug administration.
13. If female, the subject is intending to become pregnant before, during, or within 6 months after participating in this study; or intending to donate ova during such time period.
14. If male, the subject intends to donate sperm during the course of this study or for 6 months thereafter.
15. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.

7.3 Excluded Medications and Treatments

The following medications and treatments are excluded from use during the study.

- Any treatment for UC or CD (whichever is applicable for the subject) other than those listed in Sections 7.3.1 through 7.3.3.
- Either approved or investigational biological agents for the treatment of non-IBD conditions, other than localized injections.
- Chronic NSAID use. (Note: Occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc. is permitted, as is daily use of baby or low-dose [81 to 162.5 mg] aspirin for cardiovascular and cerebrovascular prophylaxis.)
- Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.
- Prior to initiating treatment with vedolizumab IV all patients should be brought up to date with all recommended immunizations. Patients receiving vedolizumab IV may receive non-live vaccines (e.g., subunit or inactivated vaccines). There are no data on the secondary transmission of infection by live vaccines in patients receiving vedolizumab IV. There are no data on the safety of COVID-19 vaccines in patients receiving vedolizumab IV. Live vaccines or COVID-19 vaccines may be administered concurrently with the study drug at the investigator's discretion.

7.3.1 Permitted Medications and Treatments Prior to Week 52 Procedures

Subjects are permitted to receive a therapeutic dose of the following medications and treatments prior to completing all necessary study procedures at Week 52. Dose reduction or discontinuation per label will be allowed only due to adverse reactions. For oral corticosteroids, as per Section 7.3.3.

- Oral 5-ASAs, if stable dose for 2 weeks immediately before the first dose of study drug.
- Oral corticosteroids: Prednisolone at a stable dose ≤ 20 mg/day, budesonide at a stable dose ≤ 6 mg/day or equivalent, provided that the dose has been stable for 4 weeks immediately before the first dose of study drug if corticosteroids had just been initiated, or for the 2 weeks immediately before the first dose of study drug if corticosteroids were being tapered (permitted under guidelines described in Section 7.3.3).
- Azathioprine or 6-mercaptopurine, provided the dose had been stable for 8 weeks immediately before the first dose of study drug.
- Methotrexate for the treatment of CD, provided the dose had been stable for 8 weeks immediately before the first dose of study drug.
- Probiotics if stable dose for 2 weeks immediately before the first dose of study drug.
- Antidiarrheals for control of chronic diarrhea. It is strongly recommended that the dose remains stable.
- Enteral feeding (≤ 900 kcal/day) for the treatment of CD, provided the dose has been stable for the 4 weeks immediately before the first dose of study drug. The dose may be modified at and after Week 12; however, it should preferably remain the stable dose and must not exceed the dose at Week 0.
- Antibiotics used for the treatment of CD, provided that the dose has been stable for the 2 weeks immediately before the first dose of study drug.

7.3.2 Permitted Medications and Treatments After Week 52 Procedures

Subjects are permitted to receive the following medications and treatments after completing all necessary study procedures at Week 52. Unless specified, initiation, discontinuation, dose increase or dose reduction of these medications and treatments are permitted at the investigator's discretion.

- Oral 5-ASAs.
- Oral corticosteroids: Prednisolone at a stable dose ≤ 30 mg/day, budesonide at a stable dose ≤ 9 mg/day or equivalent.
- Topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories.
- Azathioprine or 6-mercaptopurine.

- Methotrexate for the treatment of CD.
- Probiotics.
- Antidiarrheals for control of chronic diarrhea.
- Enteral feeding (≤ 900 kcal/day) for the treatment of CD.
- Antibiotics for the treatment of CD.
- Chinese herbal medicines for the treatment of UC or CD.
- Leukocytapheresis or granulocytapheresis.

7.3.3 Oral Corticosteroid Tapering

After completing all necessary study procedures at Week 12, subjects receiving oral corticosteroids who achieved clinical response must begin a corticosteroid tapering regimen. The recommended tapering schedule is as follows:

- For a prednisolone-equivalent dose of >10 mg/day, the dose should be reduced at a rate of 5 mg per week until a 10 mg/day dose is reached.
- For a prednisolone-equivalent dose of ≤ 10 mg/day or once a 10 mg/day dose is achieved by tapering, the dose should be reduced at a rate of 2.5 mg/week until discontinuation.
- For budesonide, the dose should be tapered at a rate of 3 mg every 3 weeks.

After Week 12 and prior to Week 24, subjects who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms may have their corticosteroids back to the original dose at Week 0. In such instances, the tapering regimen must be reinitiated within 4 weeks.

After Week 24, subjects who continue to use oral corticosteroids from prior to Week 24 must not exceed a dose of 5 mg/day of prednisolone, 3 mg/day of budesonide or equivalent. Attempts to taper and discontinue corticosteroids should continue, if clinically indicated.

Oral corticosteroid use after Week 52 should follow the guidance in Section 7.3.2.

7.3.4 Rescue Therapy

In this study, any new medication or treatment, any increase in dose of a baseline medication, or any major surgical intervention required to treat new or unresolved symptoms for UC or CD (whichever is applicable for the subject) is considered as a rescue therapy, except for the following.

- Initiation of medications or treatments or increase in dose of medications listed in Section 7.3.2.
- An increase in corticosteroid dose back to the Week 0 dose for subjects undergoing corticosteroid tapering within the guidelines presented in Section 7.3.3.

- Abscess drainage or the Seton method for anal lesions

Rescue therapy should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise subject safety.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form ([e]CRF) using the following categories. For screen failure subjects, refer to Section 9.1.17.

1. Adverse event (AE).
 - Subjects who experiences an AE may require ET because continued participation imposes an unacceptable risk to subject's health, or the subject is unwilling to continue because of the AE.
 - Subjects with abnormal liver test results should be evaluated to determine whether study drug should be continued, interrupted, or discontinued. See [Appendix C](#).
 - Leukopenia or Lymphopenia: WBC and lymphocyte counts will be monitored for all subjects. Azathioprine or 6-mercaptopurine, if applicable, should be discontinued and the dose of study drug held for an absolute lymphocyte count $<0.5 \times 10^9/L$ 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 study drug can be administered only if the absolute lymphocyte count is $\geq 0.5 \times 10^9/L$. If the absolute lymphocyte count remains $<0.5 \times 10^9/L$, study drug should be discontinued, and the subject withdrawn from the study.
2. Significant protocol deviation. The discovery that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the (e)CRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category, Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category)
5. Study termination. The sponsor, institutional review board (IRB), or Regulatory Agency terminates the study.

6. Pregnancy. The subject is found to be pregnant.

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

7. 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.

The subject should be discontinued from the study if the following criteria apply:

- The subject meets the criteria for disease worsening after Week 12.
- The subject is unable to meet the requirements described in Sections 7.3.1 through 7.3.3.
- The subject needs a rescue therapy.

Disease worsening is defined as follows:

- UC cohort: Disease worsening is defined as meeting at least one of the below criteria.
 - An increase in partial Mayo score ≥ 3 points from the Week 12 value on 1 visit (or an increase to 9 points on 1 visit if the Week 12 value > 6) and a partial Mayo score of ≥ 5 points. The investigator must be certain that the increase in partial Mayo score is attributed to UC only. If the increase in partial Mayo score is not considered to be related to UC, the subject can continue this study.
 - An increase in partial Mayo score ≥ 3 points from the Week 12 value on 2 consecutive visits (or an increase to 9 points on 2 consecutive visits if the Week 12 value > 6) and a partial Mayo score of ≥ 5 points.
- CD cohort: Disease worsening is defined as meeting at least one of the below criteria.
 - An increase in CDAI score of ≥ 100 points from the Week 12 value on 1 visit and a CDAI score of ≥ 220 points. The investigator must be certain that the increase in CDAI is attributed to CD only. If the increase in CDAI is not considered to be related to CD, the subject can continue this study.
 - An increase in CDAI score of ≥ 100 points from the Week 12 value on 2 consecutive visits and a CDAI score of ≥ 220 points.

8. Other.

Note: The specific reasons should be recorded in the “specify” field of the (e)CRF.

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject’s study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject’s participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all

procedures scheduled for the ET Visit and Final Safety Follow-up Visit. Discontinued or withdrawn subjects will not be replaced.

In case of a subject discontinuation or withdrawal from study treatment, he/she will be encouraged to continue the study and complete all the relevant study visits and assessments.

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8.0 CLINICAL STUDY MATERIAL MANAGEMENT

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

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to vedolizumab IV.

8.1.1.1 Study Drug

The study sites will be supplied by the sponsor or designee with the following medication in an open-label manner: vedolizumab 300 mg IV/vial, for single use, in 20 mL vials. The study medication will be provided in a glass vial as a lyophilized solid formulation for reconstitution using sterile water for injection. Each vial will be packaged in an appropriately labeled single vial carton. Sites provide all other materials for infusion. Additional reference information and administration instructions can be found in the pharmacy manual.

Vedolizumab IV drug product contains vedolizumab at 60 mg/mL, which is the active pharmaceutical ingredient, and the following excipients: histidine/histidine-hydrochloride (HCl), arginine-HCl, sucrose, and polysorbate 80. No novel excipients are present, and all excipients meet compendial quality standards.

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. Vedolizumab IV must be stored at 2°C to 8°C and protected from light. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

Vedolizumab 300 mg will be administered as an IV infusion over 30 minutes at Weeks 0, 4, and 8 in the treatment phase in an unblinded manner. Subjects who entered into the extension phase will receive vedolizumab 300 mg IV at Week 12 and Q4W thereafter in an unblinded manner until the date of marketing approval of vedolizumab IV Q4W, study termination, or withdrawal from study.

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 adverse events [AEs]) will be documented on an overdose page of the (e)CRF, 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 CRF(s) 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 by the investigator based on symptoms.

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will receive treatment according to the study schedule. The subject identification (ID) number will be entered onto the (e)CRF.

The investigator or investigator's designee will access the interactive web response system (IWRS) at screening to register a subject and obtain a subject identification number to identify the subject throughout the study. The investigator or the investigator's designee will use the IWRS to enroll the subject into the study. The medication ID number of the investigational drug to be dispensed will then be provided by the IWRS as well as at subsequent visits. If sponsor-supplied drug is lost or damaged, the site can request a replacement from IWRS. Refer to the appropriate study manual provided separately for additional information.

8.3 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.

The on-site pharmacist (site designee) will receive the pharmacy manual created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug vedolizumab. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug vedolizumab, and collection of unused medications from the subject as well as return of them to the sponsor or destruction of them.

The on-site pharmacist (site designee) will immediately return unused study drugs to the sponsor after the study is closed at the study site.

The IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed. Refer to Pharmacy Manual for detailed/additional instructions.

9.0 STUDY PLAN

9.1 Study Procedures

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

9.1.1 Informed Consent Procedure

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

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

A unique subject ID number will be assigned to each subject at the time the signed informed consent is obtained; this subject ID number will be used throughout the study.

Subjects under 20 years old (18 years old or above) are included in this clinical trial. The investigator is responsible for obtaining written informed consent not only from the under-aged subjects, but also from their legally acceptable representatives.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth and sex as described by the subject, height, weight, and smoking status of the subject at screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved within 1 year prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8).

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

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. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

9.1.4 Weight, Height, and Body Mass Index

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The body mass index (BMI) is calculated using metric units with the formula provided

below: Height is recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place. BMI should be derived as:

$$\text{Metric: BMI} = \text{weight (kg)} / \text{height (m)}^2$$

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then $\text{BMI} = 79.2 / 1.76^2 = 25.56818 \text{ kg/m}^2$.

The values should be reported to 1 decimal place by rounding. Thus, in the above example BMI would be reported as 25.6 kg/m².

9.1.5 Vital Sign Procedure

Vital signs will include body temperature (infra-axillary) measurement, respiratory rate, sitting blood pressure (systolic and diastolic, resting more than 5 minutes), and pulse (bpm).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

On dosing day, vital signs will be taken predose.

9.1.6 Primary Efficacy Measurement

9.1.6.1 The Patient Diary

Diary entries will be made daily by subjects from screening to end-of-study and will be used for Mayo score or CDAI calculation. At screening, subjects will be instructed on how to appropriately complete the daily diary. The symptoms of UC or CD must be recorded throughout the study, including the screening phase. Diary entries will be made daily by the subject through a validated electronic system.

For UC, in addition to the subject reported Mayo subscore components, subjects will use the validated electronic system to enter daily absolute stool frequency.

Because the endoscopy preparation can interfere with the assessment of other clinical parameters, diary entries used to calculate the complete Mayo score for UC and CDAI for CD should not be taken from the day before (the preparation day), the day of, and the day after the endoscopy is performed.

Entries should be reviewed and monitored by the study staff (see the appropriate Study Manual).

9.1.6.2 Complete Mayo Score, Modified Mayo Score and Partial Mayo Score

- “Complete Mayo score” is the sum of all the subscores, ranging from 0 to 12.
- “Modified Mayo score” is the sum of 3 subscores of stool frequency, rectal bleeding, and Mayo endoscopic subscore (findings on endoscopy), ranging from 0 to 9.

- “Partial Mayo score” is the sum of 3 subscores of stool frequency, rectal bleeding, and physician’s global assessment, ranging from 0 to 9.

The Mayo score for the assessment of UC activity is calculated as shown in [Appendix D](#).

At baseline, Mayo scores (complete Mayo score, modified Mayo score and partial Mayo score) will be obtained within 10 days prior to enrollment, using patient diary entries within the 10 days prior to enrollment, endoscopy results obtained between 14 and 5 days prior to enrollment that are centrally read, and the physician’s global assessment of the patient. These assessments will be the baseline Mayo scores for disease activity assessment.

9.1.6.3 Calculation of the Mayo Endoscopic Subscore

Endoscopy will be performed in the rectum and sigmoid colon. Of note, considering the invasiveness of endoscopy, for patients who had undergone endoscopy prior to providing informed consent, video obtained during the endoscopy may be used for the assessment of baseline Mayo scores, provided that a clear video exists and that baseline Mayo scores are assessed within 14 days of performing endoscopy.

A Central Reading Committee (CRC; see Section [11.1](#)) will be established in the study, where a member (central reader) will independently assess the Mayo endoscopic subscore. Investigators should submit clear videos so that the central reader may adequately assess the Mayo endoscopic subscore. Of note, Mayo endoscopic subscores assessed by the central reader are used for endpoint analysis.

At baseline (within 10 days prior to the start of treatment phase), modified Mayo score is calculated with the Mayo endoscopic subscore assessed by the central reader. The calculated score will be the baseline modified Mayo score, with which eligibility of the patient is evaluated.

At the evaluation of the primary efficacy endpoint (Week 12), modified Mayo score is calculated with the Mayo endoscopic subscore assessed by the investigator. The calculated score will be the Week 12 modified Mayo score, with which clinical response/non-response of the subject is evaluated in comparison with the baseline modified Mayo score.

9.1.6.4 Calculation of Subscore for Physician's Global Assessment

On the day of evaluation, the investigator conducts interviews to take note of abdominal discomfort, general condition, and the principal physician’s comments (if applicable) on and the subject’s impression of disease activity. Subscores for stool frequency and rectal bleeding, and Mayo endoscopic subscore (if applicable) are also considered to evaluate the subscore for physician’s global assessment.

9.1.6.5 The CDAI Score

The CDAI score is calculated as a total of the following 8 subscores as seen in the [Appendix E](#).

The CDAI score evaluated at baseline (Week 0) will be used to determine eligibility, using subject diary entries within 10 days prior to Week 0. At a minimum, 7 days of diary data from the last 10 days prior to Week 0 will be required for the calculation of the score. Subjects will be required to complete diary entries for at least 14 days prior to Week 0.

9.1.6.6 Calculation of Hematocrit for the CDAI Score

Blood sample will be collected to obtain the hematocrit level for calculation of the CDAI score.

At baseline (Day 1), hematocrit is obtained at the study site for calculation of the baseline CDAI score, with which eligibility of the patient is evaluated. In case where hematocrit cannot be obtained at baseline (Day 1), the last hematocrit level obtained within 14 days prior to baseline (Day 1) is used instead.

At the evaluation of the primary efficacy endpoint (Week 12), hematocrit is obtained at the study site for calculation of the Week 12 CDAI score, with which clinical response/non-response will be evaluated in comparison with the baseline CDAI score. In case where hematocrit cannot be obtained on the day of evaluation of the primary efficacy endpoint (Week 12), the last hematocrit level obtained within 14 days prior to the day of evaluation is used instead.

At all evaluations except for the above, hematocrit is obtained at the study site on the day of evaluation for calculation of the CDAI score, where possible. In case where hematocrit cannot be obtained on the day of the evaluation, the last obtained hematocrit level is used instead.

Of note, hematocrit levels obtained from a central laboratory are used for endpoint analysis.

9.1.6.7 Inflammatory Bowel Disease Questionnaire (IBDQ)

The subjects will be asked to fill IBDQ before administration of the study drug on the day of study drug administration. It composed of a total of 32 questions (each has 1 to 7 points) including abdominal symptoms (10 items), general condition (5 items), emotion (12 items) and social function (5 items), will be calculated as the total scores, and performed before administration of the study drug if it is the day of study drug administration.

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 over-the-counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the (e)CRF.

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, or physical

examination abnormalities noted at screening/baseline examination, according the judgment of the investigator. The condition (i.e., diagnosis) should be described. In addition, UC or CD-related extraintestinal manifestations will be recorded in the (e)CRF.

9.1.9 Procedures for Clinical Laboratory Samples

Clinical laboratory test items as shown in Table 9-a will be determined. All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 31 mL, and the approximate total volume of blood for the study per year of participation is 169 mL for the first year and 70 mL thereafter.

Table 9-a lists the tests that will be obtained for each laboratory specimen.

Table 9-a: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells (RBC)	Albumin	Qualitative (glucose, protein, occult blood, bilirubin, ketone body, leukocyte esterase, nitrite)
White blood cells (WBC)	Alanine aminotransferase (ALT)	Urine pH
Hemoglobin	Aspartate aminotransferase (AST)	Urine specific gravity
Hematocrit	Alkaline phosphatase	Microscopic (to be obtained in the event of positive leukocyte esterase or occult blood, will include WBCs, RBCs, and cast[s])
Platelets	Amylase*	
Neutrophils	Lipase	
Eosinophils	Lactate dehydrogenase (LDH)	
Basophils	Glucose	
Lymphocytes	Total and direct bilirubin	
Monocytes	Total protein	
aPTT	Creatinine	
PT/INR	Blood urea nitrogen	
	Creatine kinase	
	γ -Glutamyl transferase (GGT)	
	Potassium	
	Sodium	
	Calcium	
	Phosphorus	
	Magnesium	
	Chloride	
	Uric acid	
Other:		
Human immunodeficiency virus antibody (HIVAb)	Urine drug and salivary alcohol screen	
Hepatitis panel, including hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), and anti-hepatitis C virus (HCV)	Fecal calprotectin	
Pharmacokinetics (PK)	Serum leucine-rich α -2 glycoprotein (LRG)	
Anti-vedolizumab antibody (AVA)	Fecal <i>C. difficile</i>	
Serum C-reactive protein (CRP)	T-SPOT for tuberculosis	
	Serum human chorionic gonadotropin (hCG) (a)	
	Urine hCG (a)	
	Follicle-stimulating hormone (FSH) (b)	
	Severe acute respiratory syndrome-associated coronavirus 2 reverse transcription-polymerase chain reaction (SARS-CoV-2 RT-PCR)	

*The samples should be preferably collected under fasted conditions.

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- (a) Only in female subjects of childbearing potential.
- (b) follicle-stimulating hormone (FSH) level will be obtained for female subjects at screening if they are postmenopausal by history (i.e., last regular menstrual cycle >1 years) and not surgically sterile. The FSH result must be >40 IU/L for the subject to be permitted not to use adequate contraception.

The central laboratory will perform laboratory tests for hematology, serum chemistries, urinalysis, tests using stool samples, and SARS-CoV-2 RT-PCR. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

For subjects with treatment-emergent ALT elevations $\geq 3 \times \text{ULN}$, see [Appendix C](#) for additional monitoring, evaluation, and follow-up recommendations.

The investigator or designee is responsible for transcribing or attaching laboratory results to the (e)CRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

9.1.10 Contraception and Pregnancy Avoidance Procedure

9.1.10.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 6 months after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (e.g., condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective method of contraception below.

If a male subject or his partner requests to change the method of contraception at any time between signing of informed consent and 6 months after the last dose of study drug, the investigator will take into account the current and the planned methods of contraception and provide guidance to the subject or his partner to ensure that contraception is achieved during the transition.

9.1.10.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 6 months 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 in Section 9.1.10.3). In addition, they must be advised not to donate ova during this period.

If a female subject or her partner requests to change the method of contraception at any time between signing of informed consent and 6 months after the last dose of study drug, the investigator will take into account the current and the planned methods of contraception and provide guidance to the subject or her partner to ensure that contraception is achieved during the transition.

9.1.10.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

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

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

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as “those, alone or in combination, that result in a low failure rate (i.e., <1% failure rate per year when used consistently and correctly)”. In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:

- Non-Hormonal Methods:
 - Intrauterine device (IUD)
 - Bilateral tubal occlusion
 - Vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success)
 - Sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. Abstinence is defined as refraining from heterosexual intercourse (i.e., penetration of vagina by penis) from 1 month prior to the first dose of the study drug until 6 months after the last dose of the study drug.
- 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 † (e.g., 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 for shorter duration until she has been on contraceptive for 3 months;
 - Oral †
 - Injectable †
 - Implantable †

† These contraception methods and pregnancy avoidance procedures are not approved in Japan.

2. Unacceptable methods of contraception are:

- Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods).
- Spermicides† only.
- Withdrawal.
- No method at all.
- Use of female and male condoms together.
- Cap†/diaphragm/sponge without spermicide† and without condom.

† These contraception methods and pregnancy avoidance procedures are not approved in Japan.

3. Subjects will be provided with information on highly effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
4. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
- a. Contraceptive requirements of the study
 - b. Reasons for use of barrier methods (i.e., condom) in males with pregnant partners
 - c. Assessment of subject compliance through questions such as
 - i. Have you used the contraception consistently and correctly since the last visit?
 - ii. Have you forgotten to use contraception since the last visit?

- iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is “yes”)
 - iv. Is there a chance you could be pregnant?
5. In addition to a negative serum/urine hCG pregnancy test at screening, female subjects of childbearing potential must also have a negative serum/urine hCG pregnancy test before receiving any dose of study medication as close as possible and before the first dose of study medication, preferably on the same day.

9.1.11 Pregnancy

Women of childbearing potential will be included in this study.

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, any pregnancies in the partner of a male subject during the study or for 6 months after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study drug, e.g., within 6 months of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0/Annex 1.

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

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

9.1.12 Pharmacokinetic Sample Collection and Analysis

9.1.12.1 Collection of Blood for Pharmacokinetic Sampling

Blood samples (one sample per scheduled time) for serum vedolizumab concentration will be collected at predose (within 30 minutes prior to dosing) according to the Schedules of Study Procedures ([Appendix A](#)).

The actual time of sample collection will be recorded on the source document and (e)CRF.

Instructions for collecting, processing, and shipping of PK samples are provided in the laboratory manual.

9.1.13 Immunogenicity Sample Collection

Blood specimens for the assessment of AVA will be collected at predose (within 30 minutes prior to dosing) as shown in the Schedule of Study Procedures ([Appendix A](#)). A sample will be assessed for neutralizing AVA, if AVA is detected.

Serum titers of AVA will be determined using a validated assay. Neutralizing AVA will be determined using a validated assay.

Please refer to the appropriate Study Manual for information on sample collection and preparation

9.1.14 Fecal Calprotectin Sample Collection

A stool sample will be collected for the analysis of fecal calprotectin, a biomarker of intestinal inflammatory activity, as shown in the Schedule of Study Procedures ([Appendix A](#)).

9.1.15 Stool Sample

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 or return of disease activity.

9.1.16 Leucine-rich α -2 glycoprotein

A blood sample will be collected for the analysis of LRG, a biomarker of intestinal inflammatory activity, as shown in Schedule of Study Procedures ([Appendix A](#)).

9.1.17 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible during screening, the investigator should contact the IWRS as a notification of screen failure and complete the Screen Failure (e)CRF.

If the subject is withdrawn at the screening visit, the investigator should complete the (e)CRF.

The primary reason for screen failure is recorded in the (e)CRF using the following categories:

- Pretreatment event (PTE)/AE.
- Did not meet inclusion criteria or did meet exclusion criteria. <specify reason>.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal <specify reason>.
- Study termination.
- Other <specify reason>.

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

9.1.18 Documentation of Study Entrance

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

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

9.2 Monitoring Subject Treatment Compliance

The study drugs dosed to the subjects will be recorded in the (e)CRF for the dates, times of start/end of the infusion. When infusion of a study drug was not completed, dosage and reasons for dose incomplete will be recorded in the (e)CRF.

9.3 Schedule of Observations and Procedures

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

9.3.1 Screening

Subjects will be screened between 28 and 3 days prior to baseline (Week 0), inclusive. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.17 for procedures for documenting screening failures.

Procedures to be completed at the screening phase include:

- Informed consent.
- Inclusion/exclusion criteria.
- Register subject in IWRS.
- Demographics, medical history, and medication history.
- Physical examination.
- Weight and height.
- Vital signs.
- Diary instructions.
- Endoscopy (UC cohort only) (within -14 to -5 days).
- Concomitant medications.
- Clinical laboratory tests.
- Urine drug and salivary alcohol screen.

- Serum pregnancy test (hCG).
- FSH.
- HBV, HCV, HIV, TB, and COVID-19 screening.
- Fecal calprotectin.
- *C. difficile* stool sample.
- PTE/AE assessment.

9.3.2 Treatment Phase

Enrollment will take place at Week 0. If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria, the subject should be enrolled using the IWRS. Subjects will be instructed on when the first dose of investigational drug will be given as described in Section 6.1. The procedure for documenting screening failures is provided in Section 9.1.17.

9.3.2.1 Week 0 (Day 1), Week 4, and Week 8 (Window period ± 7 days)

- Inclusion/exclusion criteria (only at Week 0 [Day 1])
- Enrollment IWRS (only at Week 0 [Day 1])
- Access IWRS (only at Weeks 4 and 8)
- Physical examination
- Vital signs
- Diary review
- IBDQ (Only at Week 0 [Day 1])
- Mayo subscores of stool frequency, rectal bleeding, and physician's global assessment (UC cohort only)
- CDAI score (CD cohort only)
- Concomitant medications
- Clinical laboratory tests
- Urine pregnancy test (hCG)
- Study drug dosing
- PK blood collection
- AVA blood collection
- Serum LRG

- PTE/AE assessment

9.3.2.2 Week 12 or Early Termination (Window period ± 7 days)

- Physical examination
- Vital signs
- Diary review
- IBDQ
- Endoscopy (UC cohort only)
- Mayo subscores of stool frequency, rectal bleeding, and physician's global assessment (UC cohort only)
- CDAI score (CD cohort only)
- Concomitant medications
- Clinical laboratory tests
- Urine pregnancy test (hCG)
- PK blood collection
- AVA blood collection
- Serum LRG
- Fecal calprotectin.
- PTE/AE assessment

9.3.2.3 Final Safety Follow-up Visit for Week 12 Non-Responders or Early Termination (Window period ± 14 days)

Follow-up will begin the first day after the Final Visit and will continue until 16 weeks after the last dose. One visit will take place during Follow-up, at 16 weeks after the last dose.

The following procedures will be performed and documented at the follow-up visit:

- Physical examination
- Vital signs
- Concomitant medications
- Clinical laboratory tests
- Serum pregnancy test (hCG)
- AVA blood collection

- PTE/AE assessment

9.3.2.4 *Post Study 6-Month Long-Term Follow-up Survey for Week 12 Non-Responders or Early Termination*

Upon discontinuation of or early termination from the study, all subjects will be required to participate by telephone in a 6-month long-term follow-up (LTFU) safety questionnaire (from the last dose received).

9.3.2.5 *Unscheduled Visit*

- Physical examination
- Vital signs
- Diary review
- Mayo subscores of stool frequency, rectal bleeding, and physician's global assessment (UC cohort only)
- CDAI score (CD cohort only)
- Concomitant medications
- Clinical laboratory tests
- AVA blood collection when suspected immunologically related adverse events occur
- PTE/AE assessment

9.3.3 **Extension Phase**

9.3.3.1 *Week 12 (Window period ± 7 days)*

- Access IWRS
- Study drug dosing

9.3.3.2 *Visits Every 4 Weeks From Week 12 to 48 (Window period ± 7 days)*

Mayo subscores of stool frequency, rectal bleeding, and physician's global assessment (UC cohort only), CDAI score (CD cohort only) and clinical laboratory tests are to be performed every 8 weeks, i.e., at Weeks 20, 28, 36, and 44.

- Access IWRS
- Physical examination
- Vital signs
- Diary review

- Mayo subscores of stool frequency, rectal bleeding, and physician's global assessment (UC cohort only)
- CDAI score (CD cohort only)
- Concomitant medications
- Clinical laboratory tests
- Urine pregnancy test (hCG)
- Study drug dosing
- PTE/AE assessment

9.3.3.3 *Week 52 (Window period ± 7 days)*

- Access IWRS
- Physical examination
- Vital signs
- Diary review
- Mayo subscores of stool frequency, rectal bleeding, and physician's global assessment (UC cohort only)
- CDAI score (CD cohort only)
- Concomitant medications
- Clinical laboratory tests
- Urine pregnancy test (hCG)
- Study drug dosing
- PK blood collection
- AVA blood collection
- PTE/AE assessment

9.3.3.4 *Visits Every 4 Weeks from Week 56 (Window period ± 7 days)*

Clinical laboratory tests are to be performed every 8 weeks since Week 52, i.e., at Weeks 60, 68, 76, 84, etc.

- Access IWRS
- Physical examination
- Vital signs

- Concomitant medications
- Clinical laboratory tests
- Urine pregnancy test (hCG)
- Study drug dosing
- PTE/AE assessment

9.3.3.5 Final Visit or Early Termination (Window period ± 7 days)

Diary review, Mayo subscores of stool frequency, rectal bleeding, and physician's global assessment (UC cohort only), CDAI score (CD cohort only), PK blood collection and AVA blood collection are done only if the Final Visit or ET is prior to Week 52.

- Physical examination
- Vital signs
- Diary review
- Mayo subscores of stool frequency, rectal bleeding, and physician's global assessment (UC cohort only)
- CDAI score (CD cohort only)
- Concomitant medications
- Clinical laboratory tests
- Urine pregnancy test (hCG)
- PK blood collection
- AVA blood collection
- PTE/AE assessment

9.3.3.6 Final Safety Follow-up Visit (Window period ± 14 days)

Follow-up will begin the first day after the Final Visit and will continue until 16 weeks after the last dose. One visit will take place during Follow-up, at 16 weeks after the last dose.

The following procedures will be performed and documented during each follow-up visit:

- Physical examination
- Vital signs
- Concomitant medications
- Clinical laboratory tests

- Serum pregnancy test (hCG)
- AVA blood collection
- PTE/AE assessment

9.3.3.7 *Post Study 6-Month Long-Term Follow-Up Survey*

Upon completion of or early termination from the study, all subjects will be required to participate by telephone in a 6-month LTFU safety questionnaire (from the last dose received).

9.3.3.8 *Unscheduled Visit*

- Physical examination
- Vital signs
- Mayo subscores of stool frequency, rectal bleeding, and physician's global assessment (UC cohort only) if disease exacerbation is suspected
- CDAI score (CD cohort only) if disease exacerbation is suspected
- Concomitant medications
- Clinical laboratory tests
- AVA blood collection when suspected immunologically related adverse events occur
- PTE/AE assessment

9.3.4 **Alternative Approaches to Study Procedures and Data Collection Due to Coronavirus Disease 2019 (COVID-19)**

In unavoidable circumstances, in particular the COVID-19 pandemic, that impact the study site's ability to conduct study procedures according to the Schedule of Study Procedures ([Appendix A](#)), contingency measures may be implemented. The following information provides guidance regarding changes to the study procedures that could be implemented for study subjects or study sites that are affected by the COVID-19 public health emergency. This guidance is aligned with the current guidance from global health authorities on the conduct of clinical studies during the COVID-19 pandemic.

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

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

Procedural changes due to COVID-19 may include the following:

- No routine COVID-19 testing is required during the study unless the subject has signs or symptoms of COVID-19-related disease or COVID-19 pneumonia in the opinion of the investigator or the subject has been identified by national or local public health authority as a close contact of a probable or confirmed case of COVID-19. The decision to have the subject tested for COVID-19 is left to the subject and the investigator unless required by the health authority.
- Subjects who discontinued from screening due to COVID-19-related factors but were otherwise qualified to participate in the study may be rescreened if the sponsor or designee agrees.
- All attempts should be made to perform the assessments with the subject present at the site using the visit windows. Exceptions may be granted for alternative approaches to study procedures and data collection through approval by the sponsor or designee. Such instances must be documented in the study records and may include the following:
 - Sites impacted by the COVID-19 pandemic must contact the sponsor or designee to discuss individual subject and site circumstances to obtain approval for use of alternative approaches to study procedures and data collection.
 - Sites may seek approval from the Medical Monitor to continue subjects in the study despite departure from the Schedule of Study Procedures. Principal investigators are expected to evaluate the impact to the safety of the study subjects and site personnel for subjects to continue. In evaluating such requests, the sponsor or designee will give the highest priority to the safety and welfare of the subjects. Subjects must be willing and able to continue taking study medication and remain compliant with the protocol.
- Informed Consent Procedure: If necessary, informed consent from a potential or current study participant may be obtained via verbal consent when these individuals are unable to travel to the site. Informed consent forms will be signed once the subject can return in-person to the study site.
- Visits: All visits other than the Final Safety Follow-up Visit must be done with the subject present at the study site.
 - Protocol Deviations: Any deviations from the protocol-specified procedures due to COVID-19 will be recorded as related to COVID-19.
 - Visit Window Extension: Sites may seek approval from the sponsor or designee to extend a visit window in order to conduct an on-site visit. Assessments that cannot be completed during the protocol-specified window will be recorded as a protocol deviation, and such deviations will be recorded in the study records as related to COVID-19.

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- Final Safety Follow-up Visit: The Final Safety Follow-up Visit should be performed with the subject present at the study site. Sites may seek approval from the sponsor or designee to extend a visit window in order to conduct an on-site visit. If the visit cannot be conducted on-site within the visit window granted by the sponsor or designee, sites may conduct Final Visit procedures remotely as is feasible, including using local laboratories for assessment of clinical chemistry and hematology (as specified in [Table 9-a](#)). Assessments that cannot be completed during the protocol-specified window will be recorded as a protocol deviation, and such deviations will be recorded in the study records as related to COVID-19.
- When a physical examination or other in-person procedure is needed in response to an AE, the subject should be evaluated in-person at the site per protocol if possible. If the subject cannot visit the site due to COVID-19, the site should contact the Medical Monitor.
- Discontinuation or Withdrawal from the Study or Study Medication: If a subject chooses to withdraw from the study or study medication due to personal concerns related to the COVID-19 pandemic (other than a COVID-19-related AE), this must be specified as the reason for subject withdrawal in the (e)CRF.
- Allow transfer of study subjects to study sites away from risk zones or closer to their home to sites already participating in the study or new ones.
- For subjects who are impacted, any alternative approaches to study procedures (i.e., procedures not conducted per the Schedule of Study Procedures) due to the COVID-19 pandemic must be documented in the study records as related to COVID-19. Data collected using alternative methods may be handled differently in the final data analyses. This will be documented in the SAP.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

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

10.1.2 Adverse Events

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 (e.g., 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 Pretreatment Events and Adverse Events

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 (e.g., 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 electrocardiogram [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:

- Changes in laboratory values are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., 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 and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests) 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 (e.g., “worsening of...”).
- If a subject has a pre-existing episodic concurrent medical condition (e.g., 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 (e.g., “worsening of...”).
- If a subject has a degenerative concurrent medical condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., “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 (e.g., “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 (e.g., “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.

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Preplanned procedures (surgeries or interventions):

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

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

10.1.4 Serious Adverse Events

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.

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Pretreatment events 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 Adverse Events of Special Interest

An AE of Special Interest (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation 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. Refer to Section 10.2.1.4 for information for special interest AE reporting.

10.1.6 Intensity of Pretreatment Events and Adverse Events

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 Adverse Events

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.

The start date of PTEs/AEs will be determined using the following criteria;

PTEs/AEs	Start Date
Any signs/symptoms/diseases (diagnosis)	The date that the first signs/symptoms/diseases were noted by the subject and/or the investigator should be recorded.
Asymptomatic diseases	The date when examination was performed for diagnosis and diagnosis was confirmed should be recorded. The date when diagnosis was confirmed should also be recorded even when values or findings showed previous values or findings, or the onset time can be estimated.
Worsening or complication of concurrent medical conditions or any signs/symptoms/diseases before treatment	The date that a worsening or complication of the condition was noted first by the subject and/or the investigator should be recorded.
The examination after start of the study drug showed abnormal values/findings	The date of examination when an abnormal value or findings that was judged to be clinically significant was noted should be recorded.
The examination at the start of the study drug showed abnormal values/findings and the subsequent examinations showed worsening of the symptoms	The date of examination when apparent elevation, reduction, increase or decrease was confirmed in judgment according to the trends in those values or findings should be recorded.

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 (e.g., 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 e.g., the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.13 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages; the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining “Not recovered/not resolved”.
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (e.g., 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 Adverse Events

10.2.1.1 Pretreatment Events and Adverse Events Collection Period

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

Collection of AEs will commence from the time that the subject is first administered study drug (Day 1). Routine collection of AEs will continue until Final Safety Follow-up Visit.

10.2.1.2 Pretreatment Events and Adverse Events Reporting

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

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All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the (e)CRF, 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.

10.2.1.3 Adverse Event Collection Involving Medically Anticipated Clinical Events

Ulcerative Colitis is associated with certain characteristic signs and symptoms, including diarrhea and rectal bleeding, that may be present at baseline and persist or fluctuate based on the individual subject's disease history during the course of the study. These signs and symptoms will not be collected as AEs. These characteristics of disease activity will be regularly captured in the Mayo score.

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

Crohn's Disease is associated with certain characteristic signs and symptoms, including diarrhea and abdominal pain, that may be present at baseline and persist or fluctuate based on the individual subject's disease history during the course of the study. These signs and symptoms are considered medically anticipated clinical events for the condition under study and will not be collected as AEs. These characteristics of disease activity will be regularly captured in the CDAI score.

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

For both UC and CD, extraintestinal manifestations of the subject's disease (e.g., arthralgia, arthritis, uveitis) that develop or worsen during the study are considered as AEs.

10.2.1.4 Special Interest AE Reporting

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

Hypersensitivity Reactions (Including Infusion-Related Reactions)

Currently, there is no evidence to support the routine prophylactic administration of premedication (e.g., antihistamines, corticosteroids) to subjects receiving vedolizumab; hence such premedications are unlikely to be necessary or beneficial. At the discretion of the investigator, however, subjects may be administered premedication prior to any study drug administration. Corticosteroids, if given as a premedication, should be limited to the day of administration.

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

Subjects and caregivers will be instructed to report the development of rash, hives, pruritus, flushing, urticaria, injections site pain, redness and/or swelling, etc. that may represent an administration-related reaction (i.e., infusion site reaction or infusion-related reaction) to study medication. Subjects will be asked to report administration-related AEs to the sites immediately as they are experienced or after having received appropriate medical care. Appropriate treatment and follow-up will be determined by the investigator. If signs or symptoms of an administration-related reaction are observed during the administration of study medication, it should be immediately discontinued, and the subject treated as medically appropriate. In the case of a mild reaction, study drug administration may be reinitiated (with appropriate premedication and investigator supervision) at the discretion of the investigator. Subjects with a severe or serious administration-related reaction (e.g., shortness of breath, wheezing, stridor, angioedema, life threatening change in vital signs, severe infusion site reactions) must be withdrawn from the study (see the appropriate Study Manual). In all cases of administration-related reaction, the medical monitor must be informed as soon as practical. The disposition of subjects with less severe administration-related reactions should be discussed with the medical monitor.

Serious Infections

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

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Withholding or terminating study drug administration may be considered as described in Section 7.4.

Malignancy

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

Progressive multifocal leukoencephalopathy (PML)

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 will be administered only if the possibility of PML is definitively excluded.

If the neurologist confirms PML or is unable to rule out PML, continue to withhold dosing with vedolizumab IV and contact the local medical monitor urgently. All such cases will be referred to the PML Independent Adjudication Committee (IAC) for further evaluation and recommendation on treatment continuation.

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.

Other

Other special interest AEs include liver injury which are discussed in Section 10.2.3.

10.2.2 Collection and Reporting of Serious Adverse Events

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

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

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.

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

The SAE (e)CRF should be completed within 24 hours of first onset or notification of the event. However, as a back-up, if required, the SAE Form should be completed and reported to Takeda Pharmacovigilance or designee within 24 hours to the attention of the contact listed in Annex 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 Test Results

For any subject with ALT $\geq 3 \times$ ULN **AND** total bilirubin $> 2 \times$ ULN **OR** INR > 1.5 for which an alternative etiology has not been found, report the event as an SAE, contact the Medical Monitor within 24 hours, and follow the additional monitoring, evaluation, and follow-up recommendations in [Appendix C](#).

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. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

10.3.1 Safety Reporting to Investigators, IRBs and Regulatory Authorities

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

11.0 STUDY-SPECIFIC COMMITTEES

Because review of clinical data and assessments and decisions on the efficacy of study drug will be done by the sponsor and/or designee, Data Monitoring Committee will not be established for this study.

11.1 Central Reading Committee

The CRC will comprise independent experts with experience and training appropriate for reviews of the clinical endpoints. The members will check all results of endoscopy reported by the study sites for adjudication of Mayo endoscopic score as one of the endpoints for the UC cohort, which will be reported to the Sponsor. The CRC's assessment of each potential endpoint will be documented in the clinical database and will be used in the endpoint analysis. The purpose and responsibility will be included in the written procedures for the CRC.

11.2 PML Independent Adjudication Committee

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

12.0 DATA HANDLING AND RECORD KEEPING

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

12.1 Electronic CRFs

Completed (e)CRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply study sites with access to (e)CRFs. The sponsor will train appropriate site staff in the use of the (e)CRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. Electronic CRFs must be completed in English.

Reasons for significant corrections should additionally be included. All new additions are to be made with the date and sign, or sign and seal affixed.

The principal investigator must review the (e)CRFs for completeness and accuracy and must e-sign the appropriate (e)CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the (e)CRFs.

The following data will not be recorded into the (e)CRFs;

1. BMI
2. Laboratory test values (except urine pregnancy test)
3. Serum concentrations of vedolizumab
4. Neutralizing antibody assessment

After the lock of the study database, any change of, modification of or addition to the data on the (e)CRFs should be made by the investigator with use of change and modification records of the (e)CRFs/(e)CRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

The (e)CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the (e)CRFs. The completed (e)CRFs 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 and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific

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

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

The investigator and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, all original signed and dated informed consent forms and query responses/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.

The investigator and the head of the study site are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of ET or completion of the study.

In addition, the investigator and the head of the study site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

All statistical analysis will be performed separately for UC and CD cohorts. No pooled analysis of the cohorts will be performed in the Clinical Study Reports.

A statistical analysis plan (SAP) for the UC cohort will be prepared and finalized prior to the first subject enrolled in the UC cohort and amendments will be finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The same procedure will be performed in the SAP for the CD cohort.

A data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

UC Cohort

- Full Analysis Set (FAS): All subjects who received at least one dose of study drug
- Safety Analysis Set: All subjects who received at least one dose of study drug
- Per Protocol Set (PPS): All FAS subjects who did not have any of major protocol deviations

All decisions to exclude subjects from FAS for the PPS will be specified in the SAP.

CD Cohort

- Full Analysis Set (FAS): All subjects who received at least one dose of treatment period study drug.
- Safety Analysis Set: All subjects who received at least one dose of treatment period study drug.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demography and other baseline characteristics will be summarized and will be listed.

Descriptive statistics will be used to summarize data for continuous variables like age and weight (number of subjects [N], mean, median, standard deviations [SD], Q1, Q3, minimum, and maximum) and for categorical variables like sex (number and percentage of subjects within each category).

Medical history and concurrent medical conditions will be summarized by system organ class and preferred term and will be listed. Medication history and concomitant medications will be summarized by preferred term and will be listed.

13.1.3 Efficacy Analysis

13.1.3.1 Primary Efficacy Analysis

UC Cohort

For the primary endpoint, which is the proportion of subjects with clinical response at Week 12, point estimate and the 2-sided 95% exact confidence interval (CI) using the Clopper-Pearson method will be calculated. Missing data for the primary endpoint will be imputed using non-responder imputation method. An IA will be performed when the first 30 subjects complete assessments at Week 12 or ET. Based on the number of responders for the primary endpoint at IA, the decision (efficacy stopping, futility stopping or enrollment continuation) using statistical testing will be made according to the Table 13-a. In the case of enrollment continuation, the re-estimated sample size is shown in Table 13-b. Statistical testing at final analysis (FA) for primary endpoint will be performed according to the Table 13-b. The UC cohort may be completed with only between 31 and 59 subjects; in this case the FA will be performed according to the criteria provided in Table 13-c. Stage 1 is defined as the period between the enrollment of the first subject and the completion of assessments at Week 12 or ET of the 30th subject (sorted by the date of first study drug administration and the subject number [i.e., if 2 or more subjects have the same date of the first study drug administration, the subject with the smallest subject ID number should be selected for the 30th subject]), and stage 2 (if applicable) is defined as the period between the enrollment of the 31st subject and the completion of assessments at Week 12 or ET of the last enrolled subject in the re-estimated sample size (Note: Subjects will be sorted by the date of the first study drug administration and given subject ID numbers in ascending order). The IA will be performed using subjects enrolled in stage 1. The FA for the primary endpoint will be performed using subjects enrolled in stage 1 and stage 2 (if applicable). The re-estimated sample sizes and the corresponding criteria for statistical significance are determined according to the conditional error function by Englert and Kieser, 2012 [20] and the promising zone approach by Mehta and Pocock, 2011 [21]. The statistical testing at FA will be conducted based on number of responders in both stages (k_1+k_2) and the criteria to conclude statistical significance in Table 13-b or Table 13-c, as applicable given the final sample size. The decision criteria in Table 13-a and the criteria for concluding statistical significance in Table 13-b and Table 13-c were selected to keep $\alpha < 0.025$.

Table 13-a: Decisions at Interim Analysis

Number of Responders at Interim Analysis (k_1)	Decision
$k_1 \leq 7$	Futility stopping
$8 \leq k_1 \leq 12$	Enrollment continuation
$13 \leq k_1 \leq 30$	Efficacy stopping (statistically significance)

Table 13-b: Re-estimated Sample Size and Criteria to Conclude Statistical Significance at Final Analysis for the Primary Endpoint

Number of Responders at Interim Analysis (k ₁)	Re-estimated Sample Size (Sample Size in Stage 2)	Criteria to Conclude Statistical Significance at Final Analysis*
8	135 (105)	k ₁ +k ₂ >37 (k ₂ >29)
9	88 (58)	k ₁ +k ₂ >25 (k ₂ >16)
10	60 (30)	k ₁ +k ₂ >18 (k ₂ >8)
11	60 (30)	k ₁ +k ₂ >18 (k ₂ >7)
12	60 (30)	k ₁ +k ₂ >18 (k ₂ >6)

k₂: Number of responders in stage 2

k₁+k₂: Number of responders at final analysis for the primary endpoint

* alpha=0.025 (one-sided) is kept using those criteria.

Table 13-c: Re-estimated Sample Size and Criteria to Conclude Statistical Significance at Final Analysis for the Primary Endpoint (N ≥31)

Re-estimated Sample Size (Sample Size in Stage 2)	Criteria to Conclude Statistical Significance at Final Analysis*
31-36 (1-6)	k ₁ +k ₂ >13
37-41 (7-11)	k ₁ +k ₂ >14
42-45 (12-15)	k ₁ +k ₂ >15
46-50 (16-20)	k ₁ +k ₂ >16
51-55 (21-25)	k ₁ +k ₂ >17
56-59 (26-29)	k ₁ +k ₂ >18

k₁: Number of responders in stage 1

k₂: Number of responders in stage 2

k₁+k₂: Number of responders at final analysis for the primary endpoint

* alpha=0.025 (one-sided) is kept using those criteria.

If the criterion for futility stopping is met, the study will be terminated for the UC cohort only (i.e., the study will continue for CD cohort).

If additional subjects are enrolled over the re-estimated sample size, those subjects will not be included in the statistical test for the FA. The point estimate of the response rate using all subjects will be provided descriptively as a secondary analysis for primary endpoint.

The primary endpoint will be listed.

CD Cohort

For the primary endpoint, which is the proportion of subjects with clinical response at Week 12, point estimate and the 2-sided 95% exact CI will be calculated. Missing data for the primary endpoint will be imputed using non-responder imputation method.

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The primary endpoint will be listed.

13.1.3.2 Secondary Efficacy Analysis

The secondary endpoints will be summarized descriptively and will be listed.

13.1.4 Pharmacokinetic Analysis

Individual trough serum concentrations of vedolizumab will be presented in a data listing and summarized by each visit using descriptive statistics (arithmetic mean, SD, coefficient of variation, median, minimum, maximum, and geometric mean).

13.1.5 Pharmacodynamic Analysis

Not applicable.

13.1.6 Immunogenicity Analyses

The proportion of subjects with positive AVA (transient and persistent) and proportion of subjects with positive neutralizing AVA during the study will be also summarized and listed.

A positive AVA subject is defined as a subject who has at least 1 positive AVA result in any postbaseline sample, and is further categorized as:

- Transiently positive: defined as subjects with confirmed at least 1 positive AVA sample, and no consecutive positive AVA samples.
- Persistently positive: defined as subjects with confirmed positive AVA in 2 or more consecutive positive AVA samples at post-dose visits.

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

13.1.7 Safety Analysis

All safety endpoints will be summarized using the safety analysis set. No statistical testing or inferential statistics will be generated.

All AEs will be coded using MedDRA and be listed. Treatment-emergent AEs (TEAEs) will be summarized using preferred term and primary system organ class. A TEAE is defined as an AE that occurs on or after the start of study drug administration. Percentage of subjects who experience at least 1 TEAE will be calculated within the following analyses.

- The frequency of all TEAEs.
- The frequency of drug-related TEAEs.
- The frequency of TEAEs by intensity.
- The frequency of drug-related TEAEs by intensity.
- The frequency of TEAEs leading to study drug discontinuation.

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- The frequency of serious TEAEs.
- The frequency of TEAEs over time.
- SAEs, AESIs and deaths will be separately summarized.

Unless stated otherwise, baseline for safety endpoint is defined as the last measurement collected before study drug administration of this study (Day 1), and summary statistics will be performed for observed values and change from baseline if deemed appropriate. Shift tables may be provided for appropriate safety assessment.

13.1.8 Missing Data Analysis

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

For the primary analysis in UC cohort, sensitivity analysis may be conducted to assess the impact of dropouts for different missing mechanisms using a hybrid approach where discontinuation due to AE or lack of efficacy will be imputed as non-responder (under MNAR) and other discontinuation/missing will be imputed using multiple imputation (under MAR or MCAR).

Missing data for continuous endpoints will be imputed using last available postbaseline observation carried forward (LOCF) method. For subjects without any non-missing postbaseline measurement, the missing data will be imputed using baseline observation carried forward method.

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

13.2 Interim Analysis and Criteria for Early Termination

For the UC cohort, an IA is planned for the primary endpoint during the study. The IA will be performed when the first 30 subjects complete assessments at Week 12 or ET. If the test for the primary endpoint at the IA is statistically significant, it is concluded that the efficacy of vedolizumab IV Q4W has been confirmed, and enrollment will be stopped (efficacy stopping) and the study will continue until Final Safety Follow-up Visit with subjects enrolled by the IA. If the test for the primary endpoint at the IA satisfies the futility stopping criterion, it is concluded that the efficacy of vedolizumab IV Q4W could not have been confirmed anymore and the study will be terminated for the UC cohort only (futility stopping). In these cases, the IA will be the FA for the primary endpoint. In the case except for efficacy stopping and futility stopping, enrollment will be continued, and the sample size may be re-estimated based on the result of the IA (adaptive sample size re-estimation). After assessments of the re-estimated number of subjects, or the sponsor determined number of subjects, at Week 12 or ET are complete, the FA for the primary endpoint will be performed. Then, the FA for the entire study will be performed when all scheduled assessments of all subjects take place.

To protect the study from operational bias, study statisticians will not inform the number of responders by modified Mayo score at Week 12 with the study team nor the study

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sites/investigators until a decision is made to terminate the study or conduct the FA. In addition, study sites/investigators will not be notified of the result of the IA and the re-estimated sample size until decision is made to terminate the study or conduct the FA.

No IA is planned for the CD cohort.

13.3 Determination of Sample Size

UC Cohort

The statistical objective for the efficacy in UC cohort is to demonstrate that the proportion of subjects with clinical response at Week 12 based on modified Mayo score is statistically significantly greater than the threshold of 20%.

A study with 60 subjects will provide at least 90% power compared to the threshold rate of 20% using binomial test, assuming the true proportion of subjects with clinical response at Week 12 of 40%. An IA will be performed when the first 30 subjects complete assessments at Week 12 or ET. The decision of efficacy stopping, futility stopping or enrollment continuation will be made based on the statistical testing for the primary endpoint at IA. Sample size re-estimation will be also performed in the case of enrollment continuation. The UC cohort may be completed with any number of subjects greater than or equal to 31 subjects and then the FA will be performed.

The clinical response rate of 20% for the null hypothesis is determined by consulting medical experts to estimate the clinical response rate for UC patients who experienced secondary loss of response during maintenance therapy and continued the same treatment for 12 weeks. The clinical response rate of 40% for the alternative hypothesis is determined based on a post-hoc analysis of study C13008 (refer to Section 4.1.1.3 for details).

CD Cohort

The statistical objective for the efficacy in CD cohort is to achieve that the point estimate of the proportion of subjects with clinical response at Week 12 is greater than the threshold of 20% with a certain degree of precision.

A study with 23 subjects will provide at least 90% probability by binomial distribution to observe the point estimate of the proportion of subjects with clinical response at Week 12 $>20\%$ and will provide two-sided 95% CI of approximately $\pm 20\%$ assuming the point estimate of 40% based on normal approximation. The CD cohort may be completed with any number of subjects greater than or equal to 15 subjects and then the FA will be performed. For example, a study with 15 subjects will also provide at least 90% probability to observe the point estimate of the proportion $>20\%$ and will provide two-sided 95% CI of approximately $\pm 25\%$.

The clinical response rate of 20% for the null hypothesis is determined by consulting medical experts to estimate the clinical response rate for CD patients who experienced secondary loss of response during maintenance therapy and continued the same treatment for 12 weeks. The

clinical response rate of 40% for the alternative hypothesis is determined based on a post-hoc analysis of study C13008 (refer to Section [4.1.1.3](#) for details).

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14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information and review of (e)CRFs 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 can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained. The investigator should document all protocol deviations.

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 (e.g., 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 the head of the study site 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 (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the “Responsibilities of the Investigator” that are listed in [Appendix B](#). The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB 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 for approval. The IRB’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or study-specific screening activity/signing a contract for the clinical study). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent form) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation until the site receives drug/notification no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB 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, and submission of the investigator’s final status report to IRB. All IRB 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 and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted

uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he/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 approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB and the sponsor prior to use.

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

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

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

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

15.3 Subject Confidentiality

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

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

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

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, 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.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda

contact information, along with facility name, 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 the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

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Appendix A Schedule of Study Procedures (Screening and Treatment Phases)

Table A 1: Schedule of Study Procedures (Screening and Treatment Phases)

	Screening Phase		Treatment Phase				For Week 12 Non-Responders /ET	Unscheduled Visit
	Days -28 to -3	Must Occur Days -14 To -5	Week 0 (Day 1) ^a	Week 4	Week 8	Week 12/ET	Final Safety Follow-up Visit (16 weeks after the last dose) ^b	
Visit Window (Days)	N/A	N/A	N/A	±7	±7	±7	±14	N/A
Informed consent	X							
Inclusion/exclusion criteria	X		X					
Register subject in IWRS	X							
Enrollment IWRS			X					
Access IWRS				X	X			
Demographics, medical history ^c	X							
Medication history	X							
Physical exam ^c	X		X	X	X	X	X	X
Weight and height	X							
Vital signs ^c	X		X	X	X	X	X	X
Diary instruction	X							
Diary review			X	X	X	X		X
IBDQ ^c			X			X		
Endoscopy (UC cohort only)		X				X		
Mayo subscores of Stool Frequency, Rectal Bleeding, and Physician's Global Assessment (UC cohort only)			X ^d	X	X	X		X
CDAI score (CD cohort only)			X	X	X	X		X
Concomitant medications	X		X	X	X	X	X	X
Clinical laboratory tests ^c	X ^e		X	X	X	X	X	X

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	Screening Phase		Treatment Phase				For Week 12 Non-Responders /ET	Unscheduled Visit
	Days -28 to -3	Must Occur Days -14 To -5	Week 0 (Day 1) ^a	Week 4	Week 8	Week 12/ET	Final Safety Follow-up Visit (16 weeks after the last dose) ^b	
Visit Window (Days)	N/A	N/A	N/A	±7	±7	±7	±14	N/A
Urine drug and salivary alcohol screen	X ^c							
Serum pregnancy test (hCG) ^f	X ^c						X	
Urine pregnancy test (hCG) ^f			X	X	X	X		
FSH ^g	X ^c							
HBV ^h , HCV ^h , HIV ^h , TB ^h , COVID-19 Screening	X ^c							
Study drug dosing			X	X	X			
PK blood collection ⁱ			X	X	X	X		
AVA blood collection ⁱ			X	X	X	X	X	X ^j
Serum LRG			X	X	X	X		
Fecal calprotectin	X					X		
<i>C. difficile</i> stool sample	X ^c							
PTE/AE assessment ^k	X		X	X	X	X	X	X

AE = Adverse event, AVA = Anti-vedolizumab antibody, CD = Crohn's disease, CDAI = Crohn's Disease Activity Index, COVID-19 = Coronavirus disease 2019, ET = Early termination, FSH = Follicle-stimulating hormone, HBV = Hepatitis B virus, HCV = Hepatitis C virus, hCG = Human chorionic gonadotropin, HIV = Human immunodeficiency virus, IBDQ = Inflammatory Bowel Disease Questionnaire, IWRS = Interactive Web Response System, LRG = Leucine-rich α -2 glycoprotein, PK = Pharmacokinetics, PTE = Pretreatment event, TB = Tuberculosis, UC = Ulcerative colitis.

- The day of first study drug administration for Treatment period is Day 1. The day before first study drug administration for Treatment period is Day -1.
- Conduct Final Visit procedures for subjects discontinued early per Section 7.5. The end-of-study is defined as the date of the last visit of the last subject undergoing the study unless the study is stopped earlier by sponsor due to futility or for safety reasons.
- Will be performed before administration of the study drug.
- The components of the complete Mayo score to determine eligibility at Week 0 must be completed within 10 days prior to the start of treatment phase.
- Test results should be obtained by the Week 0 (Day 1) visit.
- Will be performed only in women of childbearing potential.

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- g. FSH level will be obtained for female subjects at Screening if they are postmenopausal by history (i.e., last regular menstrual cycle >1 years) and not surgically sterile. The FSH result must be >40 IU/L for the subject to be permitted not to use adequate contraception.
- h. If there is documented evidence that the subject had tested negative at the time of initiating treatment with or during treatment with vedolizumab IV, then these screening tests can be skipped.
- i. PK and AVA samples will be obtained at predose (within 30 minutes prior to dosing).
- j. Unscheduled sampling triggered by suspected immunologically related adverse events.
- k. A PTE is an event that occurred before the first dose of the study drug. An AE is an event that occurred after the first dose of the study drug.

Table A 2: Schedule of Study Procedures (Extension Phase)

		Extension Phase (For Week 12 Responders) ^a					
	Week 12	Visits Every 4 Weeks from Week 12 to 48	Week 52	Visits Every 4 Weeks from Week 56	Final Visit/ET	Final Safety Follow-up Visit (16 weeks after the last dose)	Unscheduled Visit
Visit Window (Days)	±7	±7	±7	±7	±7	±14	N/A
Access IWRS	X	X	X	X			
Physical exam	(T)	X	X	X	X	X	X
Vital signs	(T)	X	X	X	X	X	X
Diary review	(T)	X	X		X ^c		
Mayo subscores of Stool Frequency, Rectal Bleeding, and Physician's Global Assessment (UC cohort only)	(T)	X ^b	X		X ^c		X ^f
CDAI score (CD cohort only)	(T)	X ^b	X		X ^c		X ^f
Concomitant medications	(T)	X	X	X	X	X	X
Clinical laboratory tests	(T)	X ^b	X	X ^b	X	X	X
Serum pregnancy test (hCG)						X	
Urine pregnancy test (hCG)	(T)	X	X	X	X		
Study drug dosing	X	X	X	X			
PK blood collection ^d	(T)		X		X ^c		
AVA blood collection ^d	(T)		X		X ^c	X	X ^c
PTE/AE assessment	(T)	X	X	X	X	X	X

AE = Adverse event, AVA = Anti-vedolizumab antibody, CD = Crohn's Disease, CDAI = Crohn's Disease Activity Index, ET = Early termination, hCG = Human chorionic gonadotropin, PK = Pharmacokinetics, PTE = Pretreatment event, Q4W = Every 4 weeks, UC = Ulcerative colitis.

(T): obtained from the treatment phase

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- a. Subjects showing a clinical response at Week 12 can enter into the extension phase and can continue to receive vedolizumab IV starting from Week 12 and then every 4 weeks in an unblinded manner, until the date of marketing approval of vedolizumab IV Q4W, study termination, or subject withdrawal.
- b. Clinical laboratory tests, Mayo subscores (UC cohort only; Stool Frequency, Rectal Bleeding, and Physician's Global Assessment) and CDAI score (CD cohort only) are to be performed every 8 weeks from Week 12.
- c. Diary review, Mayo subscores (UC cohort only) or CDAI score (CD cohort only), PK blood samples, and AVA blood samples are to be collected at the Final Visit/ET if it is prior to Week 52.
- d. PK and AVA samples will be obtained at predose (within 30 minutes prior to dosing).
- e. Unscheduled sampling, triggered by suspected immunologically related adverse events.
- f. Unscheduled procedure, triggered by suspicion of disease exacerbation.

Appendix B Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to the sub-investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the head of the study in advance to get them accepted.
3. Prepare a written informed consent form and other written information, and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications and responsibilities of individual personnel to the investigator and study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgment related to the study.
8. Ensure in collaboration with the head of the study that sufficient medical care on all clinically significant adverse events related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study upon obtaining the consent of the subject, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the head of the study and the sponsor in writing.
11. Prepare correct and complete (e)CRFs, and submit them to the sponsor with electronic signature
12. Check and confirm the contents of (e)CRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the sponsor with electronic signature
13. Discuss any proposal from the sponsor including update of the protocol.
14. Notify the director of the site of the end of the study in writing.

Appendix C Guidance on Abnormal Liver Test Result Monitoring, Evaluation, and Follow-up

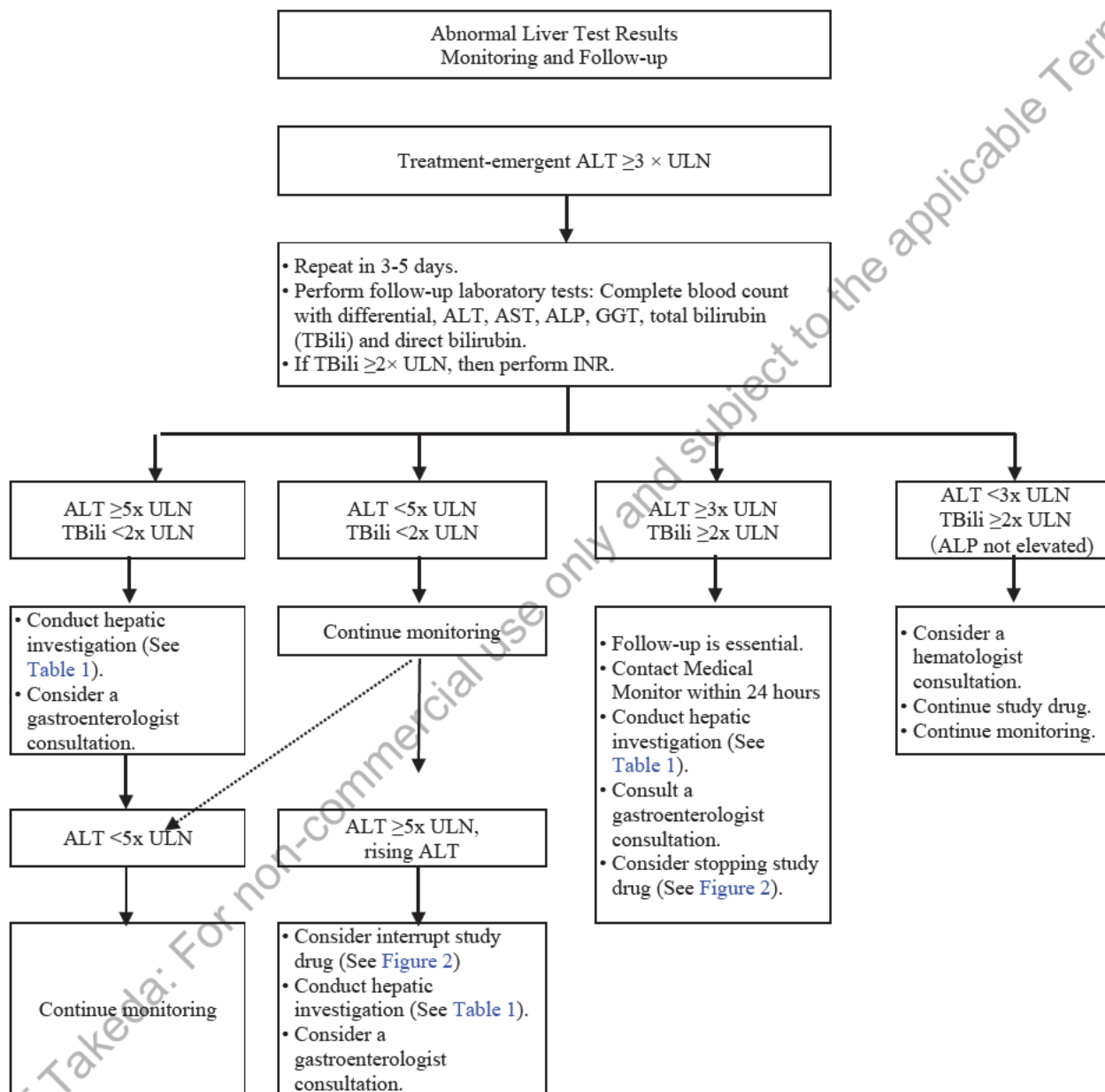
Investigators must be vigilant for abnormal liver test results in subjects during the clinical trial. Transient fluctuations in serum aminotransferases occur commonly in clinical trial subjects, but it is crucial that the investigator identifies and evaluates subjects with possible hepatic injury. This guidance is intended to aid investigations of abnormal liver test results in clinical trial subjects who had no known liver disease and had either normal or near normal baseline liver test results (i.e., ALT $<2 \times$ ULN, total bilirubin $<1.5 \times$ ULN, and ALP $<1.5 \times$ ULN) at the time of enrollment.

In evaluating trial subjects with abnormal liver test results, the investigator should perform follow-up laboratory tests to confirm the abnormal test results and monitor the subject. If the abnormal liver test results are confirmed, then the subject should be monitored and, if necessary, additional diagnostic tests should be performed as shown in Figure 1 (see below). Suggested hepatic investigations are listed in Table 1 (see below). Criteria for considering discontinuation of study drug are shown in Figure 2 (see below).

Subjects with Combined Elevations in Aminotransferase and Bilirubin

If a subject has elevated ALT $\geq 3 \times$ ULN with concurrent elevated total bilirubin $>2 \times$ ULN or elevated INR >1.5 , the investigator must contact the Medical Monitor within 24 hours. Hepatic investigations as suggested in Table 1 (see below) should be initiated. Any event of elevated ALT $\geq 3 \times$ ULN with concurrent elevated total bilirubin $>2 \times$ ULN or elevated INR >1.5 for which an alternative etiology has not been identified must be reported as an SAE.

Figure 1: Abnormal Liver Test Results: Monitoring and Follow-up

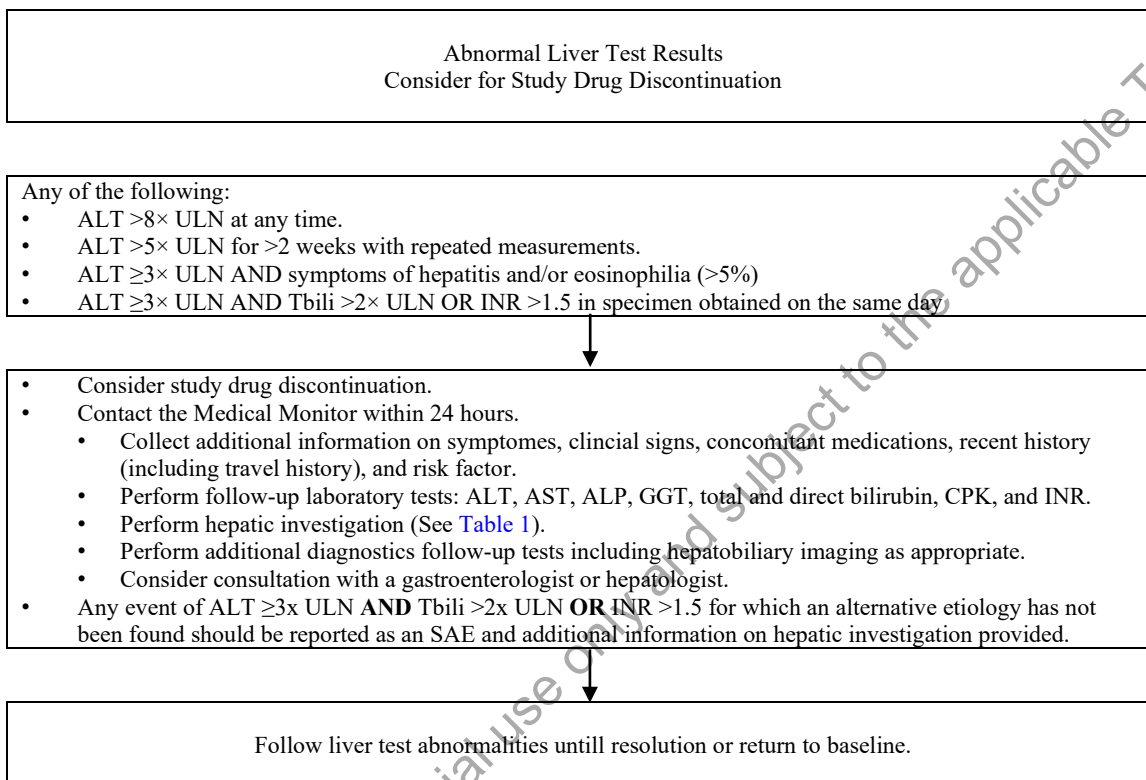


ALP, Alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; INR, international normalized ratio; Tbili, total bilirubin; ULN, upper limit of normal.

Table 1: Hepatic Investigation

Medical History	<ul style="list-style-type: none"> • Concomitant medications (including over-the-counter medications, such as acetaminophen, and herbal supplements). • Medical conditions (e.g., ischemia, hypotension, severe hypoxemia, congestive heart failure, sepsis). • Alcohol intake. • Hepatobiliary disorder. • Previous liver disease or metabolic syndrome (e.g., obesity, insulin resistance, diabetes, or dyslipidemia). • Travel history.
Physical Examination (symptoms, signs, and laboratory results)	<ul style="list-style-type: none"> • General malaise, fatigue, nausea, or vomiting. • Right upper quadrant pain or tenderness, fever, jaundice, rash. • Eosinophilia >5%.
Hepatic/Hepatobiliary imaging	<ul style="list-style-type: none"> • Perform as appropriate (e.g., abdominal ultrasound, computed tomography, magnetic resonance imaging, or other hepatobiliary imaging).
Viral hepatitis serology	<ul style="list-style-type: none"> • Hepatitis A antibody (total and IgM). • Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb), Hepatitis C antibodies (anti-HCV). • Hepatitis E (IgG and IgM). • Consider PCR for Hepatitis B, C, and E. • Consider Epstein-Barr virus serology (viral capsid antigen [VCA] nuclear antigen [EBNA], early antigen [EA]). • Consider cytomegalovirus serology (IgG and IgM).
Autoimmune hepatitis serology	<ul style="list-style-type: none"> • Anti-nuclear antibody (ANA). • Anti-smooth muscle antibody (ASMA). • Anti-liver-kidney microsomal antibody (anti-LKM).

Figure 2: Abnormal Liver Test Results: Considerations for Study Drug Discontinuation



ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGT, gamma glutamyl transferase; INR, international normalized ratio; Tbili, total bilirubin; ULN, upper limit of normal.

Appendix D: Mayo Scoring System for the Assessment of UC Activity

Stool Frequency 0: Normal number of stools for this patient 1: 1 to 2 stools more than normal 2: 3 to 4 stools more than normal 3: 5 or more stools more than normal
Rectal Bleeding 0: No blood seen 1: Streaks of blood with stool less than half the time 2: Obvious blood with stool most of the time 3: Blood alone passes
Mayo Endoscopic Subscore (Findings on Endoscopy) 0: Normal or inactive disease 1: Mild disease (erythema, decreased vascular pattern, mild friability) 2: Moderate disease (marked erythema, lack of vascular pattern, friability, erosions) 3: Severe disease (spontaneous bleeding, ulceration)
Physician's Global Assessment 0: Normal 1: Mild disease 2: Moderate disease 3: Severe Disease

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 Dec 24; 317(26):1625-1629.

Appendix E: Crohn's Disease Activity Index (CDAI) for the Assessment of CD Activity

(1) Number of liquid or very soft stools 7-day total number of liquid or very soft stools (reported on the 7 days immediately prior to the study visit)	x 2
(2) Abdominal pain 7-day total of daily abdominal pain scores on a 3-point scale: 0=none, 1=mild, 2=moderate, 3=severe (reported on the 7 days immediately prior to the study visit)	x 5
(3) General wellbeing 7-day total of daily general wellbeing scores on a 4-point scale: 0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible (reported on the 7 days immediately prior to the study visit)	x 7
(4) Extraintestinal manifestations of CD Total number of checked boxes (check all that apply): <ul style="list-style-type: none"> Arthritis/arthritis Iritis/uveitis Erythema nodosum/pyoderma gangrenosum/apthous stomatitis Anal fissure, anal fistula or perianal abscess Other fistula Fever over 37.8°C during the last week 	x 20
(5) Lomotil/Imodium/opiates for diarrhea Yes = 1, No = 0	x 30
(6) Abdominal mass None = 0, Questionable = 2, Definite = 5	x 10
(7) Hematocrit (%) (a) Males: subtract value from 47, Females: subtract value from 42	x 6
(8) Body weight (b) $(1 - [\text{Body weight} / \text{Standard Weight}]) \times 100$	x 1

CD = Crohn's Disease

(a) If hematocrit subtotal <0, enter 0.

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

Adapted from: Best WR, Backtel JM, Singleton JW, Kern Jr F. Development of Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70(3):439-444.

Appendix F Harvey-Bradshaw Index (HBI) for the Assessment of Crohn's Disease Activity

Category	Total
General Wellbeing 0 = Very Well 1 = Slightly Below Par 2 = Poor 3 = Very Poor 4 = Terrible	<input type="checkbox"/>
Abdominal Pain 0 = None 1 = Mild 2 = Moderate 3 = Severe	<input type="checkbox"/>
Number of Liquid Stools Per Day	<input type="checkbox"/>
Abdominal Mass 0 = None 1 = Dubious 2 = Definite 3 = Definite and Tender	<input type="checkbox"/>
Complications (score 1 per item) <input type="checkbox"/> Arthralgia/Arthritis <input type="checkbox"/> Uveitis/Iritis <input type="checkbox"/> Erythema nodosum <input type="checkbox"/> Aphthous ulcers <input type="checkbox"/> Pyoderma gangrenosum <input type="checkbox"/> Anal fissure <input type="checkbox"/> Draining fistula (e.g., perianal, enterocutaneous, rectovaginal) <input type="checkbox"/> Perianal Abscess	<input type="checkbox"/>
Final Score (add totals)	<input type="checkbox"/>

Adapted from: Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet.1980 Mar 8;1(8167):514.

1.3 Protocol Amendment 01 Summary of Changes

This document describes the changes in reference to the protocol incorporating Amendment 01.

The primary reasons for this amendment are to:

- Exclude from the study, subjects with lingering coronavirus disease 2019 (COVID-19) related symptoms, if previously diagnosed as having COVID-19.
- Allow HBsAg-negative, HBsAb-positive, and HBcAb-positive subjects to be enrolled into the study.
- Allow sexual abstinence as an option for contraception.
- Allow subjects and their partners to switch the method of contraception during study participation.
- Added Mayo subscores of stool frequency, rectal bleeding, and physician's global assessment (UC cohort only) and CDAI score (CD cohort only) at Extension Phase, Unscheduled Visit triggered by suspicion of disease exacerbation.
- Specify the time point at which pharmacokinetic (PK) and anti-vedolizumab antibody (AVA) samples are obtained relative to study drug dosing.
- Add AVA sample collection at Final Safety Follow-up Visit and at Unscheduled Visit triggered by suspected immunologically related adverse events.
- Remove serious adverse event (SAE) reporting in paper.
- Add a description on COVID-19 vaccines and that COVID-19 vaccines may be administered concurrently with the study drug at the investigator's discretion.
- Minor grammatical and editorial changes, as well as correction of inconsistencies and typographical errors are included for clarification purposes only.

The following is a summary of the changes made in this amendment.

Protocol Amendment 01		
Summary of Changes		
Section(s) Affected by Change	Description of Each Change and Rationale	
Location	Description	Rationale
Section 2.0 Study Summary, Main Criteria for Exclusion #4 Section 7.2.2 Infectious Disease Exclusion Criteria #1	Added the following text at the end of the sentence: "or has lingering COVID-19-related symptoms, if previously diagnosed as having COVID-19"	To exclude from the study subjects with lingering COVID-19-related symptoms, if previously diagnosed as having COVID-19.
Section 7.2.2 Infectious Disease Exclusion Criteria, #3.	Deleted "HBcAb-negative" from the definition of HBV immune subjects and added the following	To allow HBsAg-negative, HBsAb-positive, and HBcAb-positive subjects to be

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Protocol Amendment 01		
Summary of Changes		
Section(s) Affected by Change	Description of Each Change and Rationale	
Location	Description	Rationale
	text: "Investigators should follow relevant guidelines and closely monitor subjects with positive hepatitis B core antibody (HBcAb) for any signs and symptoms of HBV activation".	enrolled into the study while ensuring their safety.
Section 9.1.10.3 Definitions and Procedures for Contraception and Pregnancy Avoidance.	<p>Added the following text on sexual abstinence under non-hormonal methods: "Sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. Abstinence is defined as refraining from heterosexual intercourse (i.e., penetration of vagina by penis) from 1 month prior to the first dose of the study drug until 6 months after the last dose of the study drug."</p> <p>Deleted the text "Sexual abstinence is NOT an acceptable method of contraception" from the list of unacceptable methods of contraception.</p>	To allow sexual abstinence as an option for contraception, in light of the current contraceptive situation in Japan which has a low rate of intrauterine device and oral contraceptive usage.
Section 9.1.10.1 Male Subjects and Their Female Partners.	Added the following text: "If a male subject or his partner requests to change the method of contraception at any time between signing of informed consent and 6 months after the last dose of study drug, the investigator will take into account the current and the planned methods of contraception and provide guidance to the subject or his partner to ensure that contraception is achieved during the transition."	To allow subjects and their partners to switch the method of contraception during study participation.
Section 9.1.10.2 Female Subjects and Their Male Partners.	Added the following text: "If a female subject or her partner requests to change the method of	To allow subjects and their partners to switch the method of

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Protocol Amendment 01		
Summary of Changes		
Section(s) Affected by Change	Description of Each Change and Rationale	
Location	Description	Rationale
	contraception at any time between signing of informed consent and 6 months after the last dose of study drug, the investigator will take into account the current and the planned methods of contraception and provide guidance to the subject or his partner to ensure that contraception is achieved during the transition.”	contraception during study participation.
Section 9.3.3.8 Unscheduled Visit Table A 2: Schedule of Study Procedures (Extension Phase), Unscheduled Visit	Added the following procedures “Mayo subscores of stool frequency, rectal bleeding, and physician's global assessment (UC cohort only) if disease exacerbation is suspected” and “CDAI score (CD cohort only) if disease exacerbation is suspected” at Unscheduled Visit and referred to a new footnote ‘f’ as “Unscheduled procedure, triggered by suspicion of disease exacerbation”	To assess disease activity when disease exacerbation is suspected.
Section 9.1.12.1 Collection of Blood for Pharmacokinetic Sampling; Section 9.1.13 Immunogenicity Sample Collection; Appendix A, Table A 1: Schedule of Study Procedures (Screening and Treatment Phases); footnote i; Table A 2: Schedule of Study Procedures (Extension Phase), footnote d.	Specified that PK and AVA samples are collected at predose (within 30 minutes prior to dosing).	To allow for a more accurate interpretation of PK and AVA analysis results.
Section 9.3.2.3 Final Safety Follow-up Visit for Week 12 Non-Responders or Early	Added “AVA blood collection” at Final Safety Follow-up Visit.	To identify persistence of AVAs (if any).

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Protocol Amendment 01		
Summary of Changes		
Section(s) Affected by Change	Description of Each Change and Rationale	
Location	Description	Rationale
Termination (Window period ± 14 days); Section 9.3.3.6 Final Safety Follow-up Visit (Window period ± 14 days) Appendix A Table A 1: Schedule of Study Procedures (Screening and Treatment Phases), AVA blood collection; Table A 2: Schedule of Study Procedures (Extension Phase), AVA blood collection.		
Section 6.1 Study Design Section 9.3.2.5 Unscheduled Visit Section 9.3.3.8 Unscheduled Visit Appendix A Table A 1: Schedule of Study Procedures (Screening and Treatment Phases); footnote j; Table A 2: Schedule of Study Procedures (Extension Phase), footnote e.	Added the following procedure “AVA blood collection when suspected immunologically related adverse events occur” at Unscheduled Visit.	To assess AVA when suspected immunologically related adverse events occur.
Section 10.2.2 Collection and Reporting of Serious Adverse Events.	Removed SAE reporting in paper.	To remove unnecessary reporting procedure of the SAEs in paper for the investigator.
Section 7.3 Excluded Medications and Treatments, bullet #5.	Added the following text: “There are no data on the safety of COVID-19 vaccines in patients receiving vedolizumab IV.” In addition, added that COVID-19 vaccines may be administered concurrently with the study drug at the investigator’s discretion.	To provide the guidance to investigators on the use of COVID-19 vaccine along with the study drug.

Protocol Amendment 01		
Summary of Changes		
Section(s) Affected by Change	Description of Each Change and Rationale	
Location	Description	Rationale
Section 2.0 Study Summary, Sample Size Justification Section 13.3 Determination of Sample Size	Added the following texts: “The statistical objective for the efficacy in UC cohort is to demonstrate that the proportion of subjects with clinical response at Week 12 based on modified Mayo score is statistically significantly greater than the threshold of 20%” for UC cohort and “The statistical objective for the efficacy in CD cohort is to demonstrate that the point estimate of the proportion of subjects with clinical response at Week 12 is greater than the threshold of 20% with a certain degree of precision for CD cohort.”	To clarify that in both UC and CD cohorts the primary endpoint will be compared to the threshold of 20%.
Section 7.1 Inclusion Criteria, #5; Section 9.1.10.1 Male Subjects and Their Female Partners; Section 9.1.10.2 Female Subjects and their Male Partners; Section 9.1.10.3 Definitions and Procedures for Contraception and Pregnancy Avoidance.	Deleted the term “effective method(s)” of contraception from the text.	Correction of inconsistency. The text had remained in error when developing the initial version of the protocol.
Section 7.3 Excluded Medications and Treatments, bullet #3.	Deleted the word “and” before “menstrual cramps” and added “etc.” after “menstrual cramps.”	To clarify that NSAIDs and acetaminophen can be used for other indications in accordance with the package insert.
Section 9.1.6.2 Complete Mayo Score, Modified Mayo Score and Partial Mayo Score; Section 9.1.6.5 The CDAI Score.	Migrated in-text Table 9.a Mayo Scoring System for the Assessment of UC Activity and Table 9.b Crohn’s Disease Activity Index (CDAI) for the Assessment of CD Activity to the appendices as Appendices D and E, respectively.	To keep together all tables describing disease activity scoring in the appendix of the protocol.

Protocol Amendment 01		
Summary of Changes		
Section(s) Affected by Change	Description of Each Change and Rationale	
Location	Description	Rationale
Section 9.1.9 Procedures for Clinical Laboratory Samples Table 9-a: Clinical Laboratory Tests Section 9.3.1 Screening Appendix A Table A 1: Schedule of Study Procedures (Screening and Treatment Phases), Urine drug and salivary alcohol screen.	Updated “Urine drug and alcohol screen” as “Urine drug and salivary alcohol screen”	To clarify the study procedure of alcohol screen.
Section 9.1.11 Pregnancy	Deleted the word “not” from following sentence “Women of childbearing potential will not be included in this study”.	Typographical error: Women of childbearing potential are allowed in the study.
Section 13.1.6 Immunogenicity Analyses, bullet #1.	Clarified the definition of transiently positive subjects as subjects with confirmed at least 1 positive AVA sample, and no consecutive positive AVA samples.	To clarify the definition of transiently positive subjects.
Section 13.1.6 Immunogenicity Analyses	Added the following text: “The impact of immunogenicity on PK, efficacy and safety (including infusion site reactions and infusion related reactions) will be explored.”	To assess the impact of immunogenicity as in previous clinical trials of vedolizumab IV.
Appendix F Harvey-Bradshaw Index (HBI) for the Assessment of Crohn’s Disease Activity	Added a table describing “Harvey-Bradshaw Index (HBI) for the Assessment of Crohn’s Disease Activity”.	To provide details of HBI Assessment of Crohn’s Disease activity.
Throughout document.	Minor grammatical, editorial, administrative changes, and correction of inconsistencies and typographical errors not mentioned above.	To update the text and correct any errors for better readability.