Clinical Study Protocol

NCT Number: NCT02620046

Title: A Phase 3b Open-label Study to Determine the Long-Term Safety and Efficacy of Vedolizumab Subcutaneous in Subjects With Ulcerative Colitis and Crohn's Disease

Study Number: MLN0002SC-3030

Document Version and Date: Amendment 10.0, 20 October 2020

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

PROTOCOL

A Phase 3b Open-Label Study to Determine the Long-term Safety and Efficacy of Vedolizumab Subcutaneous in Subjects With Ulcerative Colitis and Crohn's Disease

Vedolizumab SC Long-Term Open-Label Extension Study

Sponsor: Takeda Development Center Americas, Inc.
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Study Number: MLN0002SC-3030

IND Number: 118980 **EudraCT Number:** 2015-000482-31

Compound: Vedolizumab SC

Date: 20 October 2020 **Amendment Number:** 10

Amendment History:

Date	Amendment Number	Amendment Type	Region
20 October 2020	10	Substantial	Global
24 October 2018	09	Substantial	Belgium, Denmark, Germany, Hungary, Italy, Lithuania, Poland, Romania, Spain, Sweden, United Kingdom
16 October 2018	08	Nonsubstantial	Belgium, Denmark, Germany, Hungary, Italy, Lithuania, Poland, Romania, Spain, Sweden, United Kingdom
23 April 2018	07	Substantial	Global
28 March 2018	06	Substantial	Japan
08 November 2016	05	Substantial	Global
01 August 2016	04	Substantial	Global
12 May 2016	03	Substantial	Global
10 February 2016	02	Substantial	Global
04 September 2015	01	Substantial	Global
27 February 2015	Initial Protocol	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

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

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

Contact Type/Role	**Americas, Europe, Asia and Japan TDC Contact**
Serious adverse event and pregnancy reporting	*Americas*: Fax: +1-224-554-1052 Email: PVSafetyAmericas@tpna.com *Europe/Rest of World:* Email: eupv@tgrd.com
Medical Monitor (medical advice on protocol and compound)	IQVIA Medical Services Department Tel: See Study Reference Materials
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	[redacted], MD, PhD [redacted], Clinical Science Office Telephone: [redacted] Mobile: [redacted]

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

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

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

[redacted], MD Date
[redacted], Clinical Science

[redacted], PhD Date
[redacted]
Statistics & Quantitative Sciences

[redacted], PhD, MBA Date
[redacted] Quantitative Clinical Pharmacology

INVESTIGATOR AGREEMENT

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

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

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Protocol Amendment 10 Summary of Changes

Protocol Amendment 10 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 10.

The primary reasons for this amendment are to:

- Describe the management of study procedures (eg, distribution of study medication and conduct of study visits) to maintain subject safety, confidentiality, and study integrity in the context of healthcare delivery challenges due to a pandemic (eg, coronavirus disease 2019 [COVID-19]).
- Change the frequency of clinic visits after at least Week 72 to every 24 weeks, starting at the next visit that is a multiple of 24 (eg, Week 96, 120, 144, etc), while requiring subjects to return to the site every 8 weeks between these clinic visits to receive an 8-week supply of study medication for at-home administration.
- Update the treatment duration to remove the maximum treatment duration of 5 years and to allow treatment to continue until vedolizumab SC is available in the subject's country commercially or through other access programs.
- Remove the option that subjects can switch to vedolizumab intravenous (IV) if vedolizumab subcutaneous (SC) is not available (originally proposed in protocol amendment 7; note that this option was never implemented for any subject).

This global amendment harmonizes changes from regional amendments 8 and 9 into a single global amendment. Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

A history of MLN0002SC-3030 protocol amendments 1 through 9 is provided in Appendix G.

Protocol Amendment 10		
Summary of Changes		
Section(s) Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 STUDY SUMMARY Section 5.1.2 Secondary Objectives	Combined the objectives related to patient-reported outcomes (PROs) into a single objective that includes both health-related quality of life and work productivity and activity assessments.	To clarify that PROs include assessments of both health-related quality of life and work productivity and activity.

Protocol Amendment 10		
Summary of Changes		
Section(s) Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 STUDY SUMMARY Section 6.1 Study Design Figure 6.a Schematic of Study Design Section 9.3.2 Final Visit or Early Termination Appendix A Schedule of Study Procedures, footnote g	Updated the duration of vedolizumab subcutaneous (SC) treatment to remove the maximum treatment duration of 5 years and to allow treatment to continue until vedolizumab SC is available in the subject's country commercially or through other access programs.	To ensure uninterrupted study medication availability for subjects who continue to receive clinical benefit from vedolizumab SC treatment.
Section 2.0 STUDY SUMMARY Section 5.2.2 Secondary Endpoints	Clarified that for subjects with Crohn's disease (CD), the proportion of subjects with clinical response will be summarized for randomized early terminator CD subjects only (defined as randomized CD subjects withdrawn from the parent study between Week 6 and Week 52).	Clinical response will not be summarized for randomized completer CD subjects (ie, subjects who completed the Maintenance Phase of MLN0002SC-3031) or for nonrandomized Week 14 responder CD subjects (ie, subjects who did not achieve a clinical response at Week 6 of Study MLN0002SC-3031 but who did achieve a clinical response at Week 14 after receiving a third vedolizumab intravenous (IV) infusion). CD disease activity is measured using 2 different indices in Studies MLN0002SC-3031 and MLN0002SC-3030 (Crohn's Disease Activity Index and Harvey-Bradshaw Index [HBI], respectively). For randomized completer CD subjects or nonrandomized Week 14 responder CD subjects, baseline values in Study MLN0002SC-3031 are used for comparison which are not available. Clinical remission will be evaluated for all ulcerative colitis (UC) and CD subjects.
Section 2.0 STUDY SUMMARY Section 5.2.3 Resource Utilization and Patient Reported Outcome Endpoints Section 9.1.18.2 EQ-5D Questionnaire	Corrected Euro Quality of Life-5D (EQ-5D) "utility score" or "total score" to "index score."	To ensure consistency in the use of terminology describing the EQ-5D index score to assess overall heath-related quality of life.

Protocol Amendment 10		
Summary of Changes		
Section(s) Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 STUDY SUMMARY Section 13.1.7 Safety Analysis	Removed subgroup safety analysis by concomitant medication.	To provide clarification of the planned safety analyses.
Section 2.0 STUDY SUMMARY Section 13.1.6 Resource Utilization and PRO	Clarified that time to major UC- or CD-related events will be analyzed using the Kaplan-Meier method.	To specify the analysis method for time to disease-related events.
Section 2.0 STUDY SUMMARY	[redacted]	To correct the study summary to align with the main text.
Section 4.1.2 Vedolizumab	Updated exposure data for the vedolizumab development program.	To provide the most current exposure information for vedolizumab.
Section 4.1.2.2 Clinical Experience With Vedolizumab IV	Updated the number of completed phase 1 studies, updated the text describing Study C13008 to indicate that the study is completed, and updated the total number of subjects who have died in the vedolizumab clinical program.	To provide the most current information on completed studies and safety information for the vedolizumab clinical program.
Section 4.1.2.3 Clinical Experience With Vedolizumab SC	Added a statement regarding 4 completed phase 1 studies of vedolizumab SC and added efficacy and safety results for the completed phase 3 studies of vedolizumab SC in subjects with UC and CD (Studies MLN0002SC-3027 and MLN0002SC-3031, respectively).	To provide the most current efficacy and safety information for the vedolizumab SC clinical program.
Section 4.3 Benefit:Risk Assessment	Updated text with observations of similar steady-state exposure to vedolizumab resulting in similar maintenance efficacy and safety, independent of the dosing route or presentation.	To provide the most current benefit-risk assessment of vedolizumab SC administration.
Section 6.1 Study Design	Added "the receipt of, or need for" to the definition of requirement for rescue medications for subjects in Study MLN0002SC-3030.	To align the definition of requirement for rescue medications with that of the parent studies.

Protocol Amendment 10		
Summary of Changes		
Section(s) Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 6.1 Study Design Appendix A Schedule of Study Procedures, table header and footnotes c, j, u, v	Changed the frequency of clinic visits after at least Week 72 to every 24 weeks, starting at the next visit that is a multiple of 24 (eg, Week 96, 120, 144, etc).	To reduce subject burden while maintaining sufficient safety monitoring and ensuring adequate data collection to support endpoint analyses. All enrolled subjects are estimated to have completed the Week 72 visit by the time of implementation of this amendment.
Section 6.1 Study Design Appendix A Schedule of Study Procedures, footnote q	Specified that subjects must return to the clinic every 8 weeks to receive an 8-week supply of vedolizumab SC for administration at home.	To support at-home study drug administration while enabling appropriate study drug accountability measures.
Section 6.1 Study Design Section 8.2 Investigational Drug Assignment and Dispensing Procedures	Changed the language regarding vedolizumab SC injections by subjects or caregivers from "should occur" to "may occur" under the supervision of study staff at each clinic visit.	To allow flexibility in the administration of study medication at clinic visits.
Section 6.1 Study Design Section 8.1 Study Medication and Materials Section 9.1.22 Procedure for Switching to PFS+NSD and PFS+AI	Removed the option that subjects can switch to vedolizumab IV if vedolizumab SC is not available.	To align protocol procedures across all regions with those approved in Amendment 8. This option was never implemented in any region, and no subjects in this study switched to vedolizumab IV.
Section 9.1.5 Vital Sign Procedure	Removed the specification that vital signs be obtained within 0.5 hour before a scheduled blood draw.	To remove the time restriction between the vital sign measurements and blood draws during the same visit.
Section 9.1.6.1 Diary Completion and Review Section 9.1.6.2 Collection of Subject-Reported Components of HBI Score	Clarified that partial Mayo scores for subjects with UC are calculated based on daily diary entries. Added a new Section 9.1.6.2 to clarify that HBI scores for subjects with CD are calculated using symptoms collected at the site during clinic visits using an electronic device, outside of the subject diary.	To accurately reflect the data sources for UC and CD disease activity.
Section 9.1.18 Patient Reported Outcomes Measures	Changed section heading from "Patient-Reported Outcomes Instruments" to "Patient-Reported Outcomes Measures."	To correct the nomenclature describing PRO assessments.

Protocol Amendment 10		
Summary of Changes		
Section(s) Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 9.3.7 Alternative Approaches to Study Procedures and Data Collection Due to a Pandemic Appendix A Schedule of Study Procedures, footnote a	Added guidance on alternative approaches to executing study procedures and collecting study data due to a pandemic (eg, the coronavirus disease 2019 [COVID-19] pandemic or other future similar unexpected public health concerns requiring physical distancing), including direct-to-patient shipment of study medication, use of local laboratories, and entry of subjects' reported data on behalf of the subject during telemedicine visits.	To provide flexibility in administration of study procedures during a pandemic (eg, the COVID-19 pandemic or other future similar unexpected public health concerns requiring physical distancing), while ensuring the safety of study participants, maintaining compliance with Good Clinical Practice, and minimizing risks to study integrity.
Table 10.a Takeda Medically Significant AE List	Added COVID-19–related terms to the table of Takeda Medically Significant Adverse Events (AEs).	To comply with Takeda Global Patient Safety Evaluation guidance on the medically significant AE list.
Section 13.1.5 Other Analysis	[redacted]	[redacted]
Section 13.1.5 Other Analysis	Deleted statement that additional details will be included in the statistical analysis plan.	[redacted]
Section 13.1.8 Interim Analysis	Removed "and Criteria for Early Termination" from the section heading.	To correct the heading to accurately reflect the section contents.
Appendix A Schedule of Study Procedures, footnote u	[redacted]	[redacted]

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc. Takeda Development Centre Europe, Ltd. Takeda Development Center Asia, Pte. Ltd. Takeda Pharmaceutical Company, Ltd.	**Compound:** Vedolizumab SC	
Title of Protocol: A Phase 3b Open-label Study to Determine the Long-Term Safety and Efficacy of Vedolizumab Subcutaneous in Subjects With Ulcerative Colitis and Crohn's Disease	**IND No.:** 118980	**EudraCT No.:** 2015-000482-31
Study Number: MLN0002SC-3030	**Phase:** 3b	

Study Design:

This is a phase 3b open-label extension (OLE) study to gather the long-term safety and efficacy of vedolizumab subcutaneous (vedolizumab SC) in subjects with ulcerative colitis (UC) or Crohn's disease (CD). All enrolled subjects will receive vedolizumab SC 108 mg. From this OLE study of vedolizumab SC therapy, data regarding the occurrence of important clinical events resulting from chronic vedolizumab SC administration will be obtained. Important clinical events including those related to safety and adverse events of special interest (AESIs); serious infections including opportunistic infection such as progressive multifocal leukoencephalopathy (PML), liver injury, malignancies, injection site reactions or systemic reactions and hypersensitivity) as well as efficacy (eg, maintenance of clinical remission/ clinical response, quality of life, and various other patient-reported outcome [PRO] measures) will be collected. This study will provide long-term safety data for vedolizumab SC dosing to complement the safety data gathered from Study MLN0002SC-3027 in UC subjects and Study MLN0002SC-3031 in CD subjects.

Japan only

In Japan, active enrolled subjects who have been participating in this study for at least 16 weeks will have the option to switch from administering vedolizumab SC in prefilled syringe (PFS) to administering vedolizumab SC in PFS in a needle safety device (PFS+NSD) or in an autoinjector (PFS+AI). Only participating subjects who choose to switch presentation will be randomized (1:1) to PFS+NSD or PFS+AI, and randomization will be stratified by the subject's underlying disease, UC or CD. Training is required at 2 clinic visits to start self-injection at home. Subjects will receive training on how to use PFS+NSD or PFS+AI at the clinic before the first administration with the presentation.

After switching to PFS+AI or PFS+NSD, subjects will continue with all procedures as per the study schedule during the remaining length of the OLE study. [redacted] Subjects will not be permitted to switch between PFS+NSD and PFS+AI. Subjects may be switched back to PFS if a safety concern, lack of self-injection capability, or other issue including but not limited to lack of availability of the device is identified with PFS+NSD or PFS+AI.

Primary Objectives:

- To obtain data on long term safety and tolerability on vedolizumab SC in UC or CD subjects.

Secondary Objectives:

- To obtain data on AESIs; serious infections including opportunistic infection such as PML, liver injury, malignancies, injection site reactions or systemic reactions and hypersensitivity in UC and CD subjects receiving long-term vedolizumab SC treatment.
- To obtain data on maintaining clinical response and clinical remission in UC and CD subjects receiving long-term vedolizumab SC treatment.
- To obtain data on PROs, including quality of life and work productivity and activity, in UC and CD subjects receiving long-term vedolizumab SC treatment.

<table>
<tr><td colspan="2">• To obtain data on time to major UC and CD-related events (hospitalizations, bowel surgeries, and procedures) in UC and CD subjects receiving long-term vedolizumab SC treatment.</td></tr>
<tr><td colspan="2">Subject Population: Subjects with UC or CD who participated in a prior qualified vedolizumab SC study (MLN0002SC-3027 or MLN0002SC-3031).</td></tr>
<tr><td>Number of Subjects:
Approximately 692 subjects will enter this study. Comprised of approximately 169 UC and 348 CD subjects who will have been randomized into the Maintenance Phase of Study MLN0002SC-3027 or MLN0002SC-3031 and approximately 73 UC and 102 CD non-randomized subjects who will have achieved a clinical response at Week 14 after the third vedolizumab IV infusion after not having achieved a clinical response at Week 6.</td><td>Number of Sites:
Approximately 300 sites globally</td></tr>
<tr><td>Dose Level(s):
Vedolizumab SC 108 mg</td><td>Route of Administration:
Subcutaneous</td></tr>
<tr><td>Duration of Treatment:
It is anticipated that the duration of vedolizumab SC treatment will vary by subject based on continued benefit, but will be until vedolizumab SC is available in the subject's country commercially or through other access programs, or if the subject withdraws from the study, or the sponsor decides to close the study.</td><td>Period of Evaluation:
The first dose of vedolizumab SC in this OLE study will be timed according to the last dose of study drug in the MLN0002SC-3027 or MLN0002SC-3031 studies, to maintain the trough serum concentration above the level associated with clinical efficacy of vedolizumab IV in UC and CD subjects.
• Subjects with UC or CD who completed the Maintenance Phase (Week 52 assessment) will receive vedolizumab SC 108 mg once every 2 weeks (Q2W).
• Subjects with UC or CD who withdrew early from the Maintenance Phase due to disease worsening or need for rescue medications will receive vedolizumab SC 108 mg once every week (QW).
• Subjects with UC and CD who did not achieve a clinical response at Week 6 but who did achieve a clinical response at Week 14 after having received a third vedolizumab IV infusion at Week 6 will receive vedolizumab SC 108 mg Q2W.
After the final dose of vedolizumab SC on this study (eg, due to withdrawal), subjects will complete a Final Safety Visit, 18 weeks from the last dose received. Additionally, upon completion of (or withdrawal from) this study, subjects will be required to participate in a long-term follow-up (LTFU) safety survey by telephone, 6 months after the last dose of study drug.</td></tr>
</table>

Main Criteria for Inclusion:

The subject has previously participated in Study MLN0002SC-3027 or MLN0002SC-3031, and, in the opinion of the investigator, tolerated the study drug well. Subjects who withdraw early from Study MLN0002SC-3027 or MLN0002SC-3031 must have withdrawn due to treatment failure (ie, as determined by disease worsening or need for rescue medications from Week 14 of the respective study) during the Maintenance Phase.

Main Criteria for Exclusion:

- The subject required surgical intervention for UC or CD during or after participation in Study MLN0002SC-3027 or MLN0002SC-3031, currently requires surgical intervention for inflammatory bowel disease (IBD), or is anticipated to require surgical intervention for UC or CD during this study.
- The subject has withdrawn from Study MLN0002SC-3027 or MLN0002SC-3031 due to a study drug-related adverse event (AE).

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is the subject-year–adjusted treatment emergent-related AEs and serious adverse events (SAEs) during long-term vedolizumab SC treatment.

Secondary endpoints for this study are:

- Subject-year–adjusted AESIs (including serious infections, including opportunistic infection such as PML, liver injury, malignancies, injection-site reactions or systemic reactions and hypersensitivity) during long-term vedolizumab SC treatment.
- Proportion of subjects with clinical response during long-term vedolizumab SC treatment using partial Mayo scores in UC subjects (defined as a reduction in partial Mayo score of ≥2 points and ≥25% from Baseline with an accompanying decreased in rectal bleeding score of ≥1 or absolute rectal bleeding subscore of ≤1) and Harvey-Bradshaw Index (HBI) scores in CD subjects (defined as a ≥3-point decrease in HBI score from Baseline) (randomized early terminator CD subjects only [defined as randomized CD subjects withdrawn from the parent study between Week 6 and Week 52]).
- Proportion of subjects with clinical remission during long-term vedolizumab SC treatment using partial Mayo scores in UC subjects (defined as a partial Mayo score of ≤2 and no individual subscore >1 point) and HBI scores in CD subjects (defined as an HBI score of ≤4 points).
- Resource Utilization and Patient Reported Outcome Endpoints.
- Changes from Baseline (Week 0) in Inflammatory Bowel Disease Questionnaire (IBDQ) total and subscale scores and Euro Quality of Life-5D (EQ-5D) index and visual analog scale (VAS) scores.
- Changes from Baseline (Week 0) in WPAI-UC and WPAI-CD scores.
- Time to major UC- and CD-related events (hospitalizations, surgeries, or procedures).

Statistical Considerations:

Safety:

Safety evaluations will be descriptive based on incidence, severity and type of AEs, PML checklist responses, vital signs, laboratory results and electrocardiograms (ECGs). Descriptive statistics will be calculated. Safety analyses will be performed by UC subject population (overall and separately for subjects who received vedolizumab SC and subjects who received vedolizumab IV in the Maintenance Phase of Study MLN0002SC-3027) and CD subject population.

The number and percentage of subjects with treatment-emergent AEs ([TEAEs] defined as any AEs, regardless of relationship to study drug), AESIs (serious infections including opportunistic infection such as PML, liver injury, malignancies, injection site reactions or systemic reactions and hypersensitivity), and SAEs that occur on or after the first dose date and up to 18 weeks after the last dose date of the study drug will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, high level term, and preferred term overall, by severity, and by relationship to study drug. Separate summaries will also be generated for treatment-related AEs overall and by

severity. Exposure adjusted AEs will be presented. Change from Baseline in clinical laboratory tests and vital signs will be summarized. Subjects with markedly abnormal values for laboratory tests and vital signs will be tabulated.

The LTFU safety data will be summarized descriptively.

Efficacy:

Descriptive statistics, including 95% confidence intervals, will be used in analyses of partial Mayo score (subjects with UC) or HBI score (subjects with CD). The change from Baseline in partial Mayo and HBI scores will be summarized by time point, and the means will be plotted over time. The proportion of subjects who are in clinical remission and clinical response will be summarized by time point.

PROs

Descriptive statistics will be used in analyses of IBDQ, EQ-5D, and WPAI-UC/WPAI-CD scores. Changes from Baseline in IBDQ, EQ-5D, WPAI-UC, and WPAI-CD scores will be calculated and 95% confidence intervals will be provided by time point.

Disease-related Healthcare Resource Utilization:

Time to major UC- and CD-related events (hospitalizations, surgeries and procedures) will be analyzed using Kaplan-Meier method and 95% confidence intervals will be provided.

[redacted]

Sample Size Justification:

The current estimate is that approximately 692 subjects will enter this study: 169 UC and 348 CD subjects who will have been randomized into the Maintenance Phase of Study MLN0002SC-3027 or MLN0002SC-3031; 73 UC and 102 CD subjects who will have achieved a clinical response at Week 14 after a third vedolizumab IV infusion after not having achieved a clinical response at Week 6.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

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

All institutional affiliations of the investigator and subinvestigator should be declared on their curriculum vitae, which must be provided to the sponsor prior to the start of the study.

3.2 Principal Investigator/Coordinating Investigator

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

3.3 List of Abbreviations

Term	Definition
5-ASA	5-aminosalicylate
Act-1	murine predecessor to vedolizumab antibody
AE	adverse event
AESI	adverse event of special interest
AI	autoinjector
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AVA	antivedolizumab antibody; also called HAHA
$C_{av, ss}$	average serum concentration over the dosing interval at steady state
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
C_{max}	maximum observed serum concentration
CNS	central nervous system
C_{trough}	trough serum concentration levels
DSMB	data safety monitoring board
DTP	direct-to-patient
ECG	electrocardiogram
eCRF	electronic case report form
ECL	electrochemiluminescence
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ENTYVIO; KYNTELES	vedolizumab IV
EQ-5D	Euro Quality of Life-5D
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GALT	gut-associated lymphoid tissue
GCAP	granulocytapheresis
GCP	Good Clinical Practice
GI	gastrointestinal(ly)
HAHA	human antihuman antibody
HBI	Harvey-Bradshaw Index
HCl	hydrochloride
HCP	healthcare provider
HRQOL	health-related quality of life

Term	Definition
IAC	Independent Adjudication Committee
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council on Harmonisation
ID	identification
IEC	independent ethics committee
Ig	Immunoglobin
IM	intramuscular(ly)
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous(ly)
IWRS	interactive web response system
JCV	John Cunningham virus
LCAP	leukocytapheresis
LFT	liver function test
LTFU	long-term follow-up
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MLN0002	vedolizumab
NSAID	nonsteroidal anti-inflammatory drug
NSD	needle safety device
OLE	open-label extension
PC	product complaint
PFS	prefilled syringe
PFS+AI	prefilled syringe in autoinjector
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
PTE	pretreatment event
QW	once weekly
Q2W	once every 2 weeks
Q4W	once every 4 weeks
Q8W	once every 8 weeks

Term	Definition
QOL	quality of life
RAMP	Risk Assessment and Management Program for PML
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
TNF-α	tumor necrosis factor- alpha
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VCAM-1	vascular cell adhesion molecule-1
WBC	white blood cell
WHODRUG	World Health Organization Drug Dictionary
WPAI	Work Productivity and Activity Impairment

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

3.5 Study Definitions

Term	Definition
Ulcerative Colitis Subjects	
Clinical remission	A partial Mayo score of ≤2 and no individual subscore >1 point.
Clinical response	A reduction in partial Mayo score of ≥2 points and ≥25% from Baseline with an accompanying decrease in rectal bleeding score of ≥1 or absolute rectal bleeding subscore of ≤1).
Crohn's Disease Subjects	
Clinical remission	A Harvey-Bradshaw Index (HBI) score of ≤4 points.
Clinical response	A ≥3-point decrease in HBI score from Baseline.

4.0 INTRODUCTION

4.1 Background

4.1.1 Diseases and Current Treatments

Inflammatory bowel disease (IBD) is a chronic, relapsing, inflammatory disorder of the gastrointestinal (GI) tract that includes 2 entities, namely ulcerative colitis (UC) and Crohn's disease (CD).

UC is characterized by diffuse, superficial inflammation of the colonic mucosa that begins in the rectum and extends proximally to involve any contiguous length of colon. The prevalence of UC is approximately 200/100,000 of the United States (US) population and approximately 150/100,000 of the population in Western Europe [1-3] and 63.6/100,000 of the population in Japan [4]. A genetic contribution to the disease is indicated by the increased incidence of UC (of 30 to 100 times that of the general population) among first-degree relatives of patients with UC. The characteristic pathology is one of chronic inflammation characterized by large numbers of lymphocytes and histiocytes in the diseased mucosa and submucosa with an acute inflammatory infiltrate composed of neutrophils variably present.

CD is a relapsing, remitting inflammatory disease that may involve any portion of the length of the GI tract from mouth to anus in a transmural fashion from mucosa to serosa. The prevalence of CD is approximately 150/100,000 of the US population and approximately 125/100,000 of population in Western Europe [1-3] and 21.2/100,000 of the population in Japan. The characteristic pathology involves a chronic inflammatory infiltrate consisting of neutrophils and macrophages. Hallmarks of CD include granulomatous inflammation and aphthous ulceration.

Clinical manifestations of UC include diarrhea, typically bloody, as well as abdominal pain, fecal urgency, and incontinence. Clinical manifestations of CD include diarrhea, as well as abdominal pain, fecal urgency, and incontinence. In both UC and CD systemic features such as fever, weight loss, malaise, and fatigue are indicators of more extensive disease. Extra-intestinal manifestations such as uveitis, arthritis, ankylosis spondylitis, or primary sclerosing cholangitis may also be seen in conjunction with IBD. The diagnosis of UC is usually made by the clinical presentation and key features of the history, physical examination, in combination with laboratory and imaging studies. The diagnosis of CD is usually made by histopathologic examination of endoscopic mucosal biopsy specimens obtained on ileocolonoscopy.

Current treatments have been effective for many patients with IBD but have numerous limitations for patients with moderately to severely active disease. 5-aminosalicylates (5-ASAs) are the mainstay of UC pharmacotherapy for induction and maintenance of remission for patients with mild to moderate disease, but are less effective in moderate to severe disease. [5,6]. Corticosteroids are often required for the 1/3 of patients who fail to respond to 5-ASAs [7,8].

The National Cooperative Crohn's Disease Study demonstrated a role for sulfasalazine (a 5-ASA) in moderately to severely active CD [5]. However, the efficacy of 5-ASAs in CD has been called into question by a recent meta-analysis [6]. Corticosteroids are often required for the patients who

fail to respond to 5-ASAs. While highly effective for induction of remission, corticosteroids are not recommended for the maintenance of remission in UC or CD due to significant undesirable side effects, including osteoporosis, glucose intolerance, and increased risk of infection.

Immunomodulatory agents, including 6-mercaptopurine and azathioprine, have a role in maintenance of remission of moderately to severely active UC and CD. Their relatively slow onset of action precludes their use during flares of disease, and the use of these agents has been reported to potentially increase the risk of lymphoma in patients with IBD [9]. In UC, other severe adverse events (AEs) associated with use of immunomodulators include cytopenias, hepatitis, and infection. Methotrexate has a role in the management of refractory CD; however, it also demonstrates a number of dose-limiting toxicities. Antibiotics have marginal efficacy in maintenance of remission in CD.

Intravenous (IV) cyclosporine has a role in the management of severely active UC; however, it is impractical in non-hospitalized patients, requires intense monitoring, and may cause irreversible nephrotoxicity, all of which limit its use.

Monoclonal antibodies (mAbs) directed against tumor necrosis factor-alpha (TNF-α) have been approved for the treatment of UC in many countries world-wide, including infliximab (Remicade), which is administered by IV infusion, and adalimumab (Humira) and golimumab (Simponi), which are administered by subcutaneous (SC) injection [10-12]. These agents have substantially improved the care of patients with UC by inducing and maintaining remission and decreasing the need for hospitalizations and surgeries, and other complications. Although TNF-α antagonists represent an important addition to the UC pharmacologic armamentarium, they are effective in only a subset of patients, with roughly 2/3 of patients in controlled trials not in remission at the end of the first year of therapy [13,14]. Induction of remission with infliximab occurs in only 31% to 39% of patients with UC [15] and durable clinical remission (ie, defined as clinical remission at Weeks 8, 30, and 54) occurs in only 26% of patients with UC. In addition, controlled studies have demonstrated that, after failure of 1 TNF-α antagonist, a patient's response to a second TNF-α antagonist is substantially lower [16]. The TNF-α antagonists are also associated with a number of serious safety concerns based on their suppression of systemic immunity, including reactivation of tuberculosis (TB); various bacterial, viral, fungal, and opportunistic infections; and malignancies, such as hepatosplenic T cell lymphoma [10,11].

Failure of pharmacological therapy leads to colectomy in 9% to 35% of patients with UC within 5 years. Colectomy is considered to be an important adjunct treatment for refractory UC; however, colectomy with ileal pouch anal anastomosis (the standard surgical therapy) has many limitations and is associated with its own set of complications, including high stool frequency [17], female infertility [18], and a cumulative incidence of pouchitis of 50% at 10 years [19]. The limitations of current therapies for UC indicate that there is a significant need for safer and more effective therapies.

Biologic agents, including mAbs against TNF-α, such as infliximab (Remicade), adalimumab (Humira) and certolizumab pegol (Cimzia), have proven useful for both induction and maintenance of clinical response and clinical remission in CD [10,11,20]. However, efficacy data

for both infliximab and adalimumab in CD indicate only a minority of patients having a durable response at 1 year [13,14]. Certolizumab pegol as maintenance therapy was studied only up to 26 weeks, and achieves the same modest results in the general moderately to severely active CD population with more substantial outcomes in the subgroup of patients with baseline C-reactive protein (CRP) ≥10 mg/L [14]. In addition to its modest efficacy, treatment with TNF-α antagonists has been associated with serious adverse events (SAEs) involving hypersensitivity and infection. Reactivations of latent tuberculosis (TB) [21] and disseminated histoplasmosis have been reported and, in some cases, have been fatal [22]. A new class of therapy, the integrin inhibitors, has shown promising results to date. Integrin antagonists target and disrupt the leukocyte adhesion and trafficking systems, thereby reducing inflammation. Natalizumab (Tysabri), a pan-α_4 ($\alpha_4\beta_7$ and $\alpha_4\beta_1$) integrin antagonist was approved by the Food and Drug Administration (FDA) in 2008 for use in CD patients who are refractory to standard therapy [23]. However, due to the antagonizing effect of natalizumab on $\alpha_4\beta_1$, which mediates T-cell migration into the central nervous system (CNS), bone marrow, and skin via adhesion to its ligand, vascular cell adhesion molecule-1 (VCAM-1), natalizumab therapy has been associated with increased risk of John Cunningham virus (JCV) reactivation and subsequent development of progressive multifocal leukoencephalopathy (PML). As a result, natalizumab is cautiously prescribed for the treatment of CD.

Surgical removal of highly diseased, strictured, or stenotic segments of bowel in CD is not curative. Relapse occurs in a majority of patients with CD who undergo segmental resections, and the need for additional surgery is the rule rather than the exception [24]. The limitations of current therapies for IBD indicate that there is a significant need for safer and more effective therapies.

4.1.2 Vedolizumab

Vedolizumab (also known as MLN0002) is a novel recombinant humanized mAb 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 [25-28]. As a result, vedolizumab impairs the migration of gut-homing leukocytes into GI mucosa [29] and acts as a gut-selective immunomodulator.

Vedolizumab IV (also known as ENTYVIO; KYNTELES; Vedolizumab for Injection, for Intravenous Use; Vedolizumab Powder for Concentrate for Solution for Infusion; or MLN0002 IV) has been granted marketing approval in several regions, including the US and European Union (EU). Vedolizumab IV is approved for the treatment of adult patients with moderately to severely active UC and CD, who have failed conventional treatment, such as immunomodulators, corticosteroids, or TNF-α antagonists. The approved dosing and administration regimen is 300 mg vedolizumab IV infused intravenously at Weeks 0 and 2, then once every 8 weeks (Q8W) thereafter, beginning at Week 6.

Vedolizumab SC (also known as Vedolizumab Injection, for Subcutaneous Use; Vedolizumab Solution for Injection in Pre-filled Syringe; or MLN0002 SC) is a new liquid presentation that has been developed for SC administration. To develop vedolizumab SC, the vedolizumab IV presentation was modified to ensure the long-term stability needed for a liquid product. However, the vedolizumab SC drug product composition is similar to that of the vedolizumab IV presentation after reconstitution. No changes were made that would impact the primary structure of the protein, and comparable biochemical properties and in vitro functional activity have been demonstrated. Therefore, the nonclinical and clinical information from studies with vedolizumab IV are considered relevant.

As of 19 May 2020 (data lock point), more than 6856 subjects have received at least 1 dose of vedolizumab across all studies in the clinical development program. Phase 3 placebo-controlled studies enrolled 2427 subjects with UC or CD, of whom 1434 subjects were administered 300 mg of vedolizumab IV for induction followed by once every 4 weeks (Q4W) or Q8W for up to a total of 52 weeks and 488 subjects were administered 300 mg vedolizumab for induction only [30-32]. As of 19 May 2020, vedolizumab exposure has extended for ≥12 months in 2878 subjects, ≥24 months in 1762 subjects, ≥36 months in 1176 subjects, ≥48 months in 909 subjects, ≥60 months in 718 subjects, ≥72 months in 478 subjects, ≥84 months in 292 subjects, ≥96 months in 223 subjects, and ≥108 months in 111 subjects. Based on drug shipment data as of 19 May 2020, the cumulative patient exposure to vedolizumab since its marketing approval in May 2014 is estimated to be approximately 510,259 patient-years.

Previously conducted clinical studies have characterized the efficacy, safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and immunogenicity of vedolizumab in healthy subjects and subjects with UC or CD. Please refer to the current edition of the Investigator's Brochure (IB) for the most recent data for vedolizumab.

4.1.2.1 Nonclinical

Nonclinical in vitro and in vivo studies have been conducted with vedolizumab and its murine homologue, Act-1. Act-1 has demonstrated clinical and histomorphologic evidence of efficacy in an animal model of IBD (cotton-top tamarins). Extensive nonclinical evaluations of the cardiovascular, acute, local, subchronic, chronic, immunologic, and reproductive toxicity of vedolizumab in pharmacologically responsive species (New Zealand white rabbits and cynomolgus monkeys) have been conducted and support its clinical development. Nonclinical studies also show that vedolizumab does not antagonize $\alpha_4\beta_1$ integrin [29].

A single-dose local tolerance study was conducted to determine the local irritancy potential of vedolizumab SC when administered by SC injection to rabbits. Macroscopic and histological examinations of the injection sites indicated no findings of concern with the vehicle or formulated vedolizumab SC.

4.1.2.2 Clinical Experience With Vedolizumab IV

Single- and multiple-dose PK of vedolizumab have been studied in healthy subjects and in subjects with moderately to severely active UC or CD and similar PK was observed. Vedolizumab exhibits target-mediated drug disposition; hence, its elimination is characterized by linear and nonlinear processes. Following IV infusion, vedolizumab serum concentrations generally fell in a biexponential fashion until approximately 1 to 10 µg/mL, with a linear total body clearance of approximately 0.157 L/day and a serum half-life of around 25 days. Thereafter, the serum concentrations fell in a nonlinear fashion. The volume of distribution for vedolizumab is approximately 5 L.

In subjects with moderately to severely active CD (Study C13007), including subjects who had failed treatment with 1 or more therapies including TNF-α antagonists, vedolizumab IV 300 mg at Weeks 0 and 2 (induction) followed by 300 mg either Q4W or Q8W from Week 6 through Week 52 (maintenance) demonstrated statistically significant differences in efficacy compared to placebo for both the induction phase and maintenance phase. The study met its primary endpoint for the induction phase, clinical remission at Week 6, but did not meet the second primary endpoint of enhanced clinical response (Crohn's Disease Activity Index [CDAI]-100) at Week 6 in the overall population although the treatment difference favored vedolizumab. The study did meet its primary endpoint for the maintenance phase, clinical remission at Week 52, as well as important secondary endpoints, including enhanced clinical response at Week 52 and corticosteroid-free clinical remission at Week 52 [31].

In Study C13011, vedolizumab IV (300 mg at Weeks 0, 2, and 6) was administered to subjects with moderately or severely active CD who had failed conventional therapies, including TNF-α antagonists. The primary endpoint of clinical remission at Week 6 in the TNF-α antagonist failure intent-to-treat (ITT) population was not met; however, a treatment difference was observed at Week 10 in this population. Similar treatment differences favoring vedolizumab IV were also demonstrated for the overall population and in the subgroup of subjects who were TNF-α antagonist naïve [32].

Vedolizumab has shown an acceptable safety profile based on an analysis of safety data from both completed and ongoing studies (see current edition of IB). In phase 1 and 2 clinical trials (13 completed phase 1 studies in healthy subjects and 8 completed phase 1b/2 studies in UC or CD patients), there was no consistent evidence of any dose-toxicity relationships, and vedolizumab was well tolerated. The majority of the safety data is from 3 well-controlled, phase 3 clinical studies that evaluated the safety of vedolizumab IV for up to 12 months in subjects with UC (Study C13006 [52 weeks]) or CD (Studies C13007 [52 weeks] and C13011 [10 weeks]). In addition, additional safety results are available from a completed long-term open-label extension (OLE) study (C13008), in which subjects were administered vedolizumab IV Q4W.

In the pivotal phase 3 studies (C13006 and C13007), the most common (≥5% and at a higher incidence than placebo) adverse reactions in subjects administered vedolizumab IV were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, and cough. Most SAEs have been related to exacerbations or complications of the underlying UC or

CD. For those infections that were reported more frequently in vedolizumab-treated subjects, the sites of these infections correlated with the known tissue distribution of MAdCAM-1 binding sites. Anal abscess, abdominal abscess, and gastroenteritis were the most frequently reported serious infections. Extraintestinal infections (bronchitis, pneumonia, urinary tract infection, sepsis) occurred at low frequency (<1%). A total of 4% of vedolizumab-treated subjects and 3% of placebo-treated subjects experienced an infusion-related reaction. In Studies C13006 and C13007, 10% of subjects were positive for antivedolizumab antibodies (AVA) 16 weeks following the last dose of vedolizumab. Results from the clinical program to date do not suggest an increased risk for malignancy with vedolizumab treatment. Overall, the safety profile following long-term treatment with vedolizumab IV in Study C13008 was consistent with safety in the 52-week studies.

Concomitant use of corticosteroids and/or conventional immunomodulators did not appear to be associated with any increased rate of infections based on the comparative rates of infections in the phase 3 trials among subjects who had and had not received these medications.

One death occurred in a vedolizumab-treated subject during Study C13006 and 5 deaths occurred during Study C13007, including 1 death in a placebo-treated subject. As of 19 May 2020, a total of 66 deaths from multiple causes were reported in the vedolizumab clinical development program, including the completed long-term Study C13008. Six of the 66 subjects were being treated for UC and 15 subjects for CD. The remaining 45 subjects were being treated for indications with high mortality: 39 subjects with steroid-refractory intestinal acute graft-versus-host disease, 4 subjects undergoing allogeneic hematopoietic stem cell transplantation, and 2 subjects for metastatic malignant melanoma. The causes of death varied and detailed information can be found in the current edition of the IB.

Overall, vedolizumab was well tolerated in clinical studies.

4.1.2.3 Clinical Experience With Vedolizumab SC

The feasibility of administering the vedolizumab IV formulation by alternative dosing routes SC or intramuscular (IM) injection was explored in an open-label, single dose, parallel-group bioavailability study (C13010) in healthy male subjects. In this study, 42 subjects were enrolled and 14 subjects each received a single dose of 180 mg vedolizumab IV as IV infusion (over 30 minutes), SC injections (2 × 1.5 mL × 60 mg/mL), or IM injections (2 × 1.5 mL × 60 mg/mL). Following SC administration, absorption of vedolizumab was gradual, achieving maximum concentration at 7 days post-injection (time of first occurrence of C_{max} [t_{max}]). The maximum observed serum concentration (C_{max}) following SC injection was approximately 1/3 of the C_{max} following 30 minute IV infusion. There was no difference in the terminal elimination profile of the SC cohort compared to the IV cohort, indicating that the elimination of vedolizumab is not absorption rate-limited. The absolute bioavailability of vedolizumab was approximately 75% for SC administration. Vedolizumab was well tolerated when administered at a dose of 180 mg by SC injection. Five of the 14 subjects (36%) in the IV infusion cohort and 3 of the 14 subjects (21%) in the SC cohort experienced a drug-related AE (assessed by the investigator). Most AEs were mild or moderate in severity. Three of the 14 subjects (21%) in the IV infusion cohort and 2 of the 14 subjects (14%) in the SC cohort in this study were AVA positive

using the originally developed AVA assay that was used in the phase 3 studies with vedolizumab IV. While all 3 AVA positive subjects in the IV infusion cohort had neutralizing AVA, no neutralizing AVA was observed in the SC cohort.

The bioavailability and PK of vedolizumab following a single SC injection of vedolizumab SC at 3 dose levels (54, 108, and 160 mg) relative to a single IV infusion of vedolizumab IV 300 mg was examined in a phase 1, open-label study (MLN0002SC-101). Forty-eight (24 Japanese and 24 non-Japanese) healthy, adult male and female subjects were randomized, A total of 12 subjects received a single dose of vedolizumab IV 300 mg and 36 subjects received a single dose of vedolizumab SC at 54, 108, or 160 mg (12 subjects per dose group).

The bioavailability following a single SC injection of vedolizumab SC was 75.1%, independent of the vedolizumab SC dose evaluated (54, 108, or 160 mg). Vedolizumab reached maximum serum concentrations around 1 week after a single SC injection. Vedolizumab was eliminated by both linear and nonlinear pathway following SC injection, with more rapid elimination with decreasing dose/concentration. Compared with non-Japanese subjects, Japanese subjects generally showed similar or slightly higher exposure; however, ethnicity did not have an impact on clearance or central volume of distribution based on the population PK analysis, likely due to the fact that weight was included as a covariate for various population PK parameters. Simulations further confirmed that vedolizumab SC at 108 mg every 2 weeks (Q2W) is expected to provide lower trough concentrations at steady state than vedolizumab IV 300 mg Q4W and similar steady-state exposures (average serum concentration at steady state [$C_{av,ss}$]) to that from the approved vedolizumab IV 300 mg Q8W maintenance regimen.

An electrochemiluminescence (ECL) assay has been developed to determine serum titers of AVA. This assay has improved drug tolerance as compared to the prior enzyme-linked immunosorbent assay (ELISA) method used in the vedolizumab clinical development program and, as a result, is more sensitive. Both assays were used in Study MLN0002SC-101; the ECL assay data were used in the analysis of PK and safety.

Consistent with what has been reported in the literature [33,34], the percentage of AVA positive subjects appeared to be higher among subjects who received vedolizumab SC (ECL 66.7% to 75.0%; ELISA 16.7% to 50.0%) compared with subjects who received vedolizumab IV (ECL 41.7%, ELISA 8.3%). In addition, a higher percentage of AVA positive subjects who received vedolizumab SC had persistently positive AVAs for ≥14 weeks; in 4 of these subjects, an impact on PK was observed. However, no dose-dependent trend in AVA positivity was seen. The clinical significance of these immunogenicity results is unclear, since this was a single dose study in healthy subjects.

Overall, 75.0% (36/48) of subjects had treatment-emergent adverse events (TEAEs) and the percentage of subjects with a TEAE was identical in subjects who received vedolizumab SC compared with subjects who received vedolizumab IV. All TEAEs were considered by the investigator to be mild or moderate in intensity; no TEAEs of severe intensity were reported. The percentage of subjects with mild or moderate TEAEs was similar between subjects who received vedolizumab SC and vedolizumab IV; the percentages were also similar across the dose groups.

No subjects had clinical laboratory test results, vital signs, or electrocardiogram (ECG) results that were reported as AEs. Two subjects had elevated bilirubin levels that met the predefined markedly abnormal value criteria; however, no subject had abnormal liver function test (LFT) results involving aspartate aminotransferase (AST) or alanine aminotransferase (ALT).

Two AEs of special interest were reported: 1 subject in the vedolizumab SC 108 mg group experienced erythema at the injection site on the left thigh and 1 subject in the vedolizumab SC 160 mg group experienced an injection site reaction. Both events occurred on Day 1, and were observed at the 30 minute postdose observation time point (a protocol-defined time point). In each case, the event resolved at the 1.5 hour postdose observation time point and was considered by the investigator to be mild in intensity and related to study drug. Both subjects recovered without any sequelae.

Pain was assessed by the subjects who received vedolizumab SC immediately following the SC injection and between 15 and 30 minutes following the injection. The pain assessments at 15 to 30 minutes postinjection were generally lower than the assessments recorded immediately following the injection. The maximal reported score was 6 on a scale of 0 to 10, and all but 1 score for the 15 to 30 minute postinjection time point were ≤3.

No SAEs, severe AEs, or deaths were reported in Study MLN0002SC-101. The observed AEs are consistent with the overall safety profile of vedolizumab.

In addition to Study MLN0002SC-101, 4 phase 1 bioequivalence studies in healthy subjects have also been completed (Studies VedolizumabSC-1017, VedolizumabSC-1018, VedolizumabSC-1021, and VedolizumabSC-1022). Vedolizumab SC was well tolerated with an acceptable safety profile in healthy subjects. With the exception of injection site reactions, the safety profile of vedolizumab SC was similar to vedolizumab IV among phase 1 studies. Refer to the current edition of the IB for additional information on these studies.

Vedolizumab SC has been studied in 2 phase 3, randomized, double-blind, placebo-controlled clinical studies in adult patients with UC (Study MLN0002SC-3027) or CD (Study MLN0002SC-3031). The efficacy and safety of vedolizumab SC for the treatment of adult patients with moderately to severely active UC was demonstrated in a phase 3, randomized, double-blind, placebo-controlled study evaluating efficacy endpoints at Week 52 (Study MLN0002SC-3027). In this study, enrolled subjects had failed at least 1 conventional therapy, including corticosteroids, immunomodulators, and/or TNF-α antagonists (including primary nonresponders). Subjects who achieved clinical response after 2 doses of open-label vedolizumab IV (at Week 0 and Week 2) were eligible to be randomized. For the evaluation of the Week 52 endpoints, 216 subjects were randomized and treated in a double-blind fashion (2:1:1) to one of the following regimens: vedolizumab SC 108 mg Q2W, vedolizumab IV 300 mg Q8W, or placebo. The primary endpoint, the proportion of subjects with clinical remission at Week 52, was met; a statistically significant higher remission rate at Week 52 was observed for vedolizumab SC subjects than for placebo subjects. Across the secondary endpoints, the proportion of subjects meeting the efficacy criteria was consistently greater in subjects receiving maintenance vedolizumab SC treatment. Statistically significant treatment differences favoring vedolizumab SC treatment over placebo

were observed for rates of mucosal healing at Week 52 and durable clinical response at Weeks 6 and 52. Clinically meaningful treatment differences between vedolizumab SC and placebo were also observed for durable clinical remission and corticosteroid-free remission at week 52 although these were not statistically significant.

The efficacy and safety of vedolizumab SC for the treatment of adult patients with moderately to severely active CD was demonstrated in a randomized, double-blind, placebo-controlled study evaluating efficacy endpoints at Week 52 (Study MLN0002SC-3031). In this study, enrolled subjects had inadequate response to, loss of response to, or intolerance to 1 conventional therapy, including corticosteroids, immunomodulators, and/or TNF-α antagonists (including primary nonresponders). Subjects who achieved clinical response at Week 6 after 2 doses of open-label vedolizumab IV (at Week 0 and Week 2) were eligible to be randomized. For the evaluation of the Week 52 endpoints, 409 subjects were randomized and treated in a double-blind fashion (2:1) to receive vedolizumab SC 108 mg or placebo SC Q2W. The primary efficacy endpoint was met; statistically significantly higher clinical remission rates at Week 52 were observed in the vedolizumab SC group than in the placebo group. Across multiple efficacy endpoints, including all secondary endpoints, trends favoring vedolizumab SC over placebo were observed. Although not statistically significant, for the secondary efficacy endpoint of enhanced clinical response at Week 52, the treatment difference favored vedolizumab SC treatment. A clinically meaningful effect of vedolizumab SC over placebo was observed for the secondary endpoint of corticosteroid-free remission at Week 52. A favorable trend for the efficacy of vedolizumab SC was also observed for the secondary endpoint of clinical remission at Week 52 in the TNF-α antagonist naïve subject population. Because secondary endpoints were sequentially assessed as long as they met statistical significance and because the first secondary endpoint was missed, the remaining secondary endpoints could not be formally assessed.

Safety data from the completed phase 3 placebo-controlled study in subjects with UC and CD indicate that vedolizumab SC was well tolerated with an acceptable safety profile (refer to the current edition of the IB). Except for injection site reactions, the safety profile of vedolizumab SC was consistent with that for vedolizumab IV. In both studies (MLN0002SC-3027 and MLN0002SC-3031), injection site reactions were more frequently reported in the vedolizumab SC group than in the placebo group. For both studies, the most frequent infection AEs were reported in the High Level Term of upper respiratory tract infection. The frequency of SAEs was generally similar across treatment groups within each of the studies, and no injection site reactions led to discontinuation of the study medication.

4.2 Rationale for the Proposed Study

As IV infusion may not be convenient as long-term therapy for some patients, vedolizumab SC has been developed to enable injection by patients or their caregivers.

This is a phase 3b OLE study to gather long-term efficacy and safety of vedolizumab subcutaneous (vedolizumab SC) in subjects with UC or CD. All enrolled subjects will receive vedolizumab SC 108 mg. Establishing the long-term safety and tolerability of vedolizumab SC is a key component of the clinical development program of vedolizumab SC in UC and CD. From this OLE study of

vedolizumab SC therapy, data regarding the occurrence of important clinical events resulting from chronic vedolizumab SC administration will be obtained.

The current goals of treatment include: [redacted]; induction and maintenance of endoscopic mucosal healing; potential induction and maintenance of radiological healing; prevention of surgery; maintenance of normal GI function; and prevention of disability. To achieve these goals, the therapeutic regimen should be able to treat the underlying inflammation and heal the bowel.

Modifications were made to enhance the stability of the vedolizumab SC liquid presentation, but the formulation compositions are similar to the vedolizumab IV presentation. No changes were made that would impact the primary structure of the protein, and comparable biochemical properties and in vitro functional activity have been demonstrated. Therefore, all nonclinical and clinical information from studies with vedolizumab IV is considered relevant.

The proposed vedolizumab SC maintenance dosing regimen (108 mg Q2W) was selected to provide lower steady-state trough concentrations than the vedolizumab IV Q4W regimen and similar C_{avg} steady-state exposures to that from the approved vedolizumab IV dosing regimen Q8W, and the safety and efficacy of the vedolizumab SC presentation are expected to be similar to those of vedolizumab IV, outside of expected local administration site events, such as injection site reactions.

4.3 Benefit:Risk Assessment

The proposed Study MLN0002SC-3030 is a phase 3b, OLE study designed to gather data on the long-term safety and efficacy of vedolizumab SC in subjects with UC or CD. Because IV infusion may not be convenient as long-term therapy, vedolizumab SC has been developed to ultimately enable injection by patients or their caregivers. No changes were made to the vedolizumab SC drug product composition that would impact the primary structure of the protein, and comparable biochemical properties and in vitro functional activity have been demonstrated. Therefore, the nonclinical and clinical information from studies with vedolizumab IV are considered relevant.

The study population in Study MLN0002SC-3030 is consistent with the approved vedolizumab IV label. The proposed vedolizumab SC maintenance dosing regimen (108 mg Q2W) was selected to provide similar steady-state exposure to that from the approved vedolizumab IV dosing regimen (300 mg Q8W). [redacted], independent of the dosing route or presentation. In addition, safety of the vedolizumab SC presentation is similar to that of vedolizumab IV due to similar exposure, outside of expected local administration site events, such as injection site reactions. It has also been observed that administration of vedolizumab SC [redacted] as vedolizumab IV. The observed AEs with vedolizumab SC are consistent with the vedolizumab IV safety profile.

Overall, vedolizumab SC has been well tolerated in clinical studies, including 5 phase 1 studies and 2 phase 3 studies of vedolizumab SC, and has a positive benefit-risk profile in the treatment of UC or CD.

The introduction of the AI and NSD as alternative presentations is not expected to affect the benefit-risk assessment in any meaningful way. AIs and NSDs have been widely used in chronic diseases, including IBD, to make self-injections easier for patients. AIs have been shown to increase tolerability and satisfaction with injections, as well as adherence compared with manual injection methods. NSDs reduce the risk of needle stick injuries. In addition, no significant safety concerns have been reported related to the use of AIs or NSDs.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective(s)

- To obtain data on long term safety and tolerability of vedolizumab SC in subjects with UC or CD.

5.1.2 Secondary Objectives

- To obtain data on adverse events of special interest ([AESIs]; serious infections including opportunistic infection such as PML, liver injury, malignancies, injection site reactions or systemic reactions and hypersensitivity) in UC and CD subjects receiving long-term vedolizumab SC treatment.
- To obtain data on maintaining clinical response and clinical remission in UC and CD subjects receiving long-term vedolizumab SC treatment.
- To obtain data on patient-reported outcomes (PROs), including quality of life and work productivity and activity, in UC and CD subjects receiving long-term vedolizumab SC treatment.
- To obtain data on time to major UC- and CD-related events (hospitalizations, bowel surgeries, and procedures) in UC and CD subjects receiving long-term vedolizumab SC treatment.

5.1.3 Exploratory Objectives

[redacted]

5.2 Endpoints

This study will provide long-term safety data for vedolizumab SC dosing to complement the safety data gathered from Study MLN0002SC-3027 in UC subjects and Study MLN0002SC-3031 in CD subjects. Secondary and exploratory [redacted] outcomes such as clinical remission, clinical response, [redacted] will be assessed in subgroup of subjects to whom these endpoints are relevant.

5.2.1 Primary Endpoints

- Subject-year–adjusted treatment emergent AEs and SAEs during long-term vedolizumab SC treatment.

5.2.2 Secondary Endpoints

- Subject-year–adjusted AESIs during long-term vedolizumab SC treatment.
- Proportion of subjects with clinical response during long-term vedolizumab SC treatment using partial Mayo scores (defined as a reduction in partial Mayo score of ≥2 points and ≥25% from Baseline with an accompanying decrease in rectal bleeding score of ≥1 or absolute rectal bleeding subscore of ≤1) in UC subjects and Harvey-Bradshaw Index (HBI) scores (defined as a ≥3-point decreased in HBI score from Baseline) in CD subjects (randomized early terminator CD subjects only [defined as randomized CD subjects withdrawn from the parent study between Week 6 and Week 52]).
- Proportion of subjects with clinical remission during long-term vedolizumab SC treatment using partial Mayo scores (defined as a partial Mayo score of ≤2 and no individual subscore >1 point) in UC subjects and HBI scores (defined as a HBI score of ≤4 points) in CD subjects.

5.2.3 Resource Utilization and Patient Reported Outcome Endpoints

- Changes from Baseline (Week 0) in Inflammatory Bowel Disease Questionnaire (IBDQ) total and subscale scores and EuroQol (EQ-5D) index and EQ-5D VAS scores in UC and CD subjects receiving long-term vedolizumab SC treatment.
- Changes from Baseline (Week 0) in work productivity and activity impairment scores (WPAI-UC; WPAI-CD) in UC and CD subjects receiving long-term vedolizumab SC treatment.
- Time to major UC- and CD-related events (hospitalizations, bowel surgeries, and procedures) in UC and CD subjects receiving long-term vedolizumab SC treatment.

5.2.4 Exploratory Endpoints

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 3b OLE study to gather long-term safety and efficacy of vedolizumab SC in subjects with UC and CD. All enrolled subjects will receive vedolizumab SC 108 mg. Establishing the long-term safety and tolerability of vedolizumab SC is a key component of the clinical development program of vedolizumab SC in UC and CD.

From this OLE study of vedolizumab SC therapy, data regarding the occurrence of important clinical events resulting from chronic vedolizumab SC administration will be obtained. Important clinical events including those related to safety and AESIs as well as efficacy (eg, maintenance of clinical remission/clinical response, quality of life, and various other health outcomes measures) will be collected. This study will provide long-term safety data for vedolizumab SC dosing to complement the safety data gathered from Study MLN0002SC-3027 in UC subjects and Study MLN0002SC-3031 in CD subjects.

A control group has not been included in this study based on the following considerations. First, since the observed rates of rare safety events such as those listed above can be estimated from an observational study, a controlled study is unnecessary. Second, all subjects participating in this long-term safety study will have participated in a previous MLN0002SC study.

Subjects enrolling in this OLE study will have participated in the MLN0002SC-3027 or MLN0002SC-3031 study:

- Subjects with UC or CD who completed the Maintenance Phase (Week 52) will receive vedolizumab SC 108 mg Q2W.
- Subjects with UC or CD who withdrew early from the Maintenance Phase due to disease worsening or need for rescue medications from Week 14 will receive vedolizumab SC 108 mg QW.
- Subjects with UC and CD who did not achieve a clinical response at Week 6 but who did achieve a clinical response at Week 14 after having received a third vedolizumab IV infusion at Week 6 will receive vedolizumab SC 108 mg Q2W.

Table 6.a Eligibility for Study MLN0002SC-3030 Based on Reason for Withdrawal in Studies MLN0002SC-3027 and MLN0002SC-3031

	Time Point		
Reason for Withdrawal	**Prior to Week 6**	**Weeks 6-14**	**Beyond Week 14**
Disease worsening (a)	Not applicable	Eligible	Eligible
Requires rescue medication, but does not meet criteria for disease worsening	Not applicable	Not Eligible	Eligible
AE related to study drug leading to discontinuation of study drug	Not eligible	Not eligible	Not eligible
Requires surgical intervention for UC/CD	Not eligible	Not eligible	Not eligible

(a) See Section 3.5 for study definitions.

The first dose of vedolizumab SC in this OLE study is summarized by parent study and treatment in Table 6.b for Week 52 completers or Early Terminators.

Table 6.b Time of First Vedolizumab SC Dose in MLN0002SC-3030

	First OLE Vedolizumab SC Dose (no later than)	
Treatment Arm in Parent Study	**Week 52 Completers**	**Early Terminators**
MLN0002SC-3027		
Vedolizumab IV + placebo SC	Week 54 (4 weeks after last SC dose)	4 weeks after last SC dose
Vedolizumab SC + placebo IV	Week 54 (4 weeks after last SC dose)	4 weeks after last SC dose
Placebo SC + placebo IV	Week 54 (4 weeks after last SC dose)	4 weeks after last SC dose
MLN0002SC-3031		
Vedolizumab SC	Week 54 (4 weeks after last dose)	4 weeks after last dose
Placebo SC	Week 54 (4 weeks after last dose)	4 weeks after last dose

- For the week 6 nonresponders who achieved clinical response at Week 14 after the third vedolizumab IV infusion, subjects should receive their first OLE vedolizumab SC dose as close to Week 14 of the parent study as possible (preferably within week 14 ±3 days. If this window is too challenging for the sites, dosing within week 14 ±7 days is acceptable from a PK perspective (ie, maintaining trough concentration at or above 10 µg/mL).

Disease worsening is defined as:

- In UC subjects while participating in:
  - Study MLN0002SC-3027: An increase in partial Mayo score of ≥3 points on 2 consecutive visits from the Week 6 (of MLN0002SC-3027 study) value (or an increase to 9 points on 2 consecutive visits if the Week 6 value >6) and a minimum partial Mayo score of ≥5.
  - Study MLN0002SC-3030: An increase in partial Mayo score ≥3 points on 2 consecutive visits from the Week 0 (of MLN0002SC-3030 study) value (or an increase to 9 points on 2 consecutive visits if the Week 0 value >6) and a minimum partial Mayo score of ≥5.

- In CD subjects while participating in:
  - Study MLN0002SC-3031: A ≥100-point increase in CDAI score on 2 consecutive visits from the Week 6 (of MLN0002SC-3031 study) value at any study visit and a minimum CDAI score of 220 points.
  - Study MLN0002SC-3030: A ≥4-point increase in HBI score on 2 consecutive visits from the Week 0 (of MLN0002SC-3030 study) value and a minimum HBI score of 7 points.

Requirement for rescue medications for subjects is defined as:

- In Study MLN0002SC-3027 or MLN0002SC-3031 at Week 14 of each respective study and beyond: the receipt of, or need for, any rescue medications or an increase in dose of a baseline medication required to treat new or unresolved UC or CD symptoms (other than antidiarrheals for control of chronic diarrhea). Subjects who experienced treatment failure in Study MLN0002SC-3027 or MLN0002SC-3031 only as a result of receiving rescue medications (and without meeting the definition of disease worsening) before Week 14 are not eligible for Study MLN0002SC-3030.
- In Study MLN0002SC-3030: the receipt of, or need for, any new medication to treat a new or unresolved luminal manifestation of UC or CD, with the following exceptions: oral and topical (rectal) 5-ASA treatment, oral corticosteroids per the guidelines outlined in Section 7.3.2 (Oral Corticosteroid Dosing and Tapering), azathioprine or 6-mercaptopurine in subjects with UC and methotrexate in subjects with CD, antibiotics, antidiarrheals for control of chronic diarrhea, probiotics (eg, Culturelle, *Saccharomyces boulardii*).

Subjects who have UC/CD-related surgical interventions or study drug-related AEs leading to discontinuation from Study MLN0002SC-3027 or MLN0002SC-3031 will not be eligible to enroll into Study MLN0002SC-3030.

At any time during Study MLN0002SC-3030, subjects who experience treatment failure (ie, disease worsening, requirement for rescue medications):

- While receiving vedolizumab 108 mg Q2W during this OLE study: will undergo dose escalation and continue to receive vedolizumab 108 mg QW.
- While receiving vedolizumab 108 mg QW during this OLE study: will be withdrawn from the study.

It is anticipated that the duration of vedolizumab SC treatment will vary by subject based on continued benefit, but will be until vedolizumab SC is available in the subject's country commercially or through other access programs, or if the subject withdraws from the study, or the sponsor decides to close the study. After the final dose of vedolizumab SC on the study (eg, due to withdrawal), subjects will complete a Final Safety Visit 18 weeks after the last dose received. Additionally, upon completion (or withdrawal) of this study, subjects will participate in a 6-month (from their last study drug dose) follow-up survey, at which time a questionnaire will be administered.

Initially, vedolizumab SC will be supplied as prefilled syringes (PFS). Once it is available, a PFS+AI (autoinjector) presentation will replace the PFS presentation.

The following applies regardless of the type of presentation of SC device used:

After receiving initial (Week 6 nonresponders) or refresher training from the health care provider ([HCP]; investigator or designee) on the proper SC injection technique and how to manage hypersensitivity reactions potentially associated with the injection, the subjects or their caregivers will inject the active vedolizumab SC under the supervision of the HCP at the first 2 clinic visits in this study. In addition to the subjects training and HCP supervision of the SC injection technique, the first 2 clinic visits will allow the direct observation of any potential hypersensitivity or injection site reactions associated with active SC injection and timely intervention. HCPs will have appropriate monitoring and treatment for hypersensitivity reactions available for use. Subjects who experience a severe hypersensitivity reaction associated with active SC injection will be discontinued from the study.

Clinic visits will occur at Weeks 0, 1 (QW subjects only), 2 (Q2W subjects only), 4, 8, 16, and every 8 weeks until at least Week 72 or the next visit that is a multiple of 24 (eg, Week 96, 120, 144, etc), and then every 24 weeks thereafter until the end of the study. Vedolizumab SC injections by subjects or caregivers may occur under the supervision of study staff at each clinic visit. All other scheduled doses should occur outside of the clinic. Between visits scheduled every 24 weeks, subjects will return to the clinic every 8 weeks only to receive an 8-week supply of vedolizumab SC for administration at home; no other scheduled procedures will be performed. If any assessments are needed at the study medication dispensation visit (eg, to address an AE), these assessments would be recorded as an unscheduled visit.

Subjects and their caregivers will be instructed to inject vedolizumab SC into the thigh, abdomen, or upper arm, and to rotate the injection sites. Subjects and their caregivers will be instructed that the upper arm is to be used only when the caregiver administers the SC injection. Details on the training protocol and injection technique will be included in the appropriate Study Manual. For all SC dosing occurring outside of the clinic, subjects will receive a phone call from study staff within 24 hours prior to every injection for these scheduled doses to administer the PML subjective checklist and inquire about general health status and experience with prior injection. In accordance with the Risk Assessment and Management Program for PML (RAMP), any positive PML subjective finding must be evaluated via the physician administered PML objective checklist prior to subject receiving the respective dose (refer to RAMP Site Staff Brochure). AEs reported by the subject will be handled in accordance with Section 10.0 of the protocol.

Once the PFS+AI is available, subjects will switch from administering vedolizumab SC in a PFS to administering vedolizumab SC in a prefilled syringe in an autoinjector (PFS+AI). Subjects switching to the PFS+AI device will receive training on how to use PFS+AI before starting self-injection at home. An additional clinic visit for training can be arranged as needed. After switching to PFS+AI, subjects will continue with all procedures as per the study schedule during the remaining length of the OLE study (Section 9.1.22).

If PFS+AI is not available at the site for any reason, subjects may, at the discretion of the sponsor, be provided PFS+NSD or PFS. Subjects may be switched back to PFS or PFS+NSD only at the sponsor's request if any concern or issue is identified with or PFS+AI.

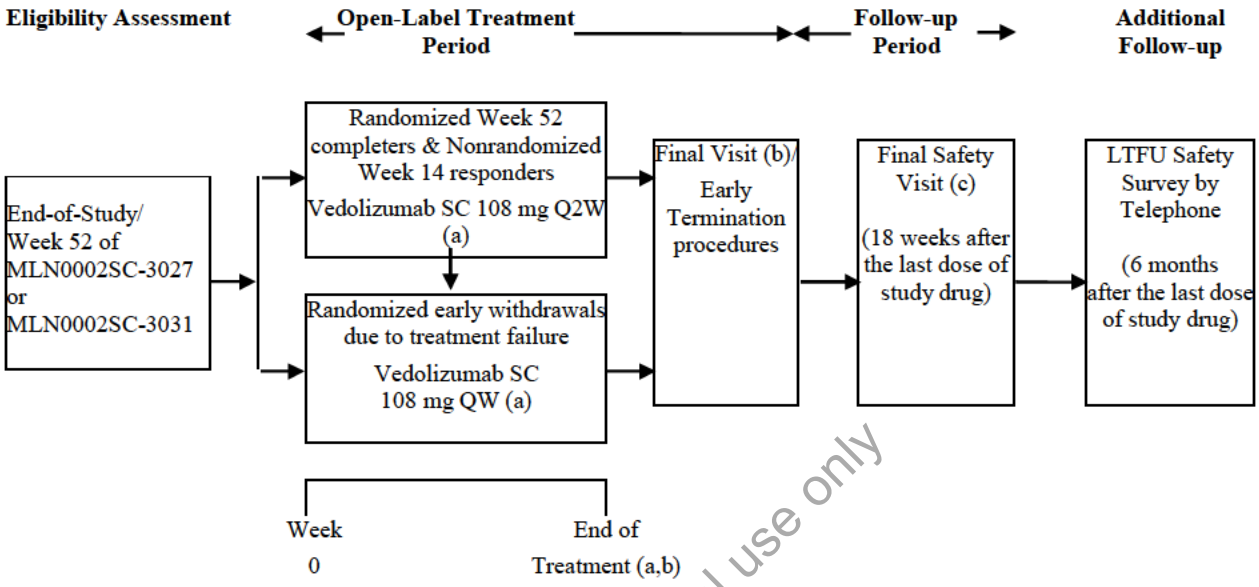
Japan Only

In Japan, active enrolled subjects who have been participating in this study for at least 16 weeks will have the option to switch from administering vedolizumab SC in PFS to administering vedolizumab SC in PFS in a needle safety device (PFS+NSD) or PFS in an autoinjector (PFS+AI). Only participating subjects who choose to switch presentation will be randomized (1:1) to PFS+NSD or PFS+AI, and randomization will be stratified by the subject's underlying disease, UC or CD. Training is required at 2 clinic visits to start self-injection at home. Subjects will receive training on how to use PFS+NSD or PFS+AI at the clinic before the first administration with the presentation. Subjects will not be permitted to switch between PFS+NSD and PFS+AI. Subjects may be switched back to PFS if a safety concern, lack of self-injection capability, or other issue including but not limited to lack of availability of the device is identified with PFS+NSD or PFS+AI (Section 9.1.22).

After switching to PFS+AI or PFS+NSD, subjects will continue with all procedures as per the study schedule during the remaining length of the OLE study. [redacted] Subjects may be switched back to PFS if any concern or issue is identified with PFS+NSD or PFS+AI (Section 9.1.22).

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



LTFU=long-term follow-up.
(a) Subjects will switch to self-injection of vedolizumab SC in PFS+AI. Once the subject has switched to administer vedolizumab SC via PFS+AI, they will continue with all study related procedures using the chosen presentation until the completion of the study or requested otherwise by the sponsor. Subjects may be switched back to PFS or to PFS+NSD only at the sponsor's request if any concern or issue is identified with PFS+AI.
Japan only: Subjects will have the option to switch to self-injection of vedolizumab SC in PFS+NSD or PFS+AI at any scheduled or unscheduled visit beginning at the Week 16 visit.
(b) Duration of vedolizumab SC treatment will vary by subject based on continued benefit, but will be until vedolizumab SC is available in the subject's country commercially or through other access programs, or if the subject withdraws from the study, or the sponsor decides to close the study.
(c) Subjects who withdraw early will return 18 weeks after the last dose of vedolizumab SC for final safety assessments at the early termination (ET) Visit.

6.2 Justification for Study Design, Dose, and Endpoints

This phase 3b OLE study is designed to gather data regarding the long-term safety and efficacy of vedolizumab SC in subjects with UC or CD.

[redacted] UC disease activity will be followed throughout this study using the partial Mayo score, a standardized measure for UC trials that includes 3 of the 4 components of the complete Mayo score [35]. CD disease activity will be followed throughout this study using the HBI, a standardized measure for CD trials that has previously been demonstrated to correlate highly with CDAI [36].

The dosing regimen used in Study MLN0002SC-3027 and MLN0002SC-3031 (vedolizumab SC 108 mg Q2W) aims to achieve similar steady-state exposure to that of the recommended

vedolizumab IV dosing maintenance regimen (300 mg Q8W) in the phase 3 registration studies (C13006 and C13007). The vedolizumab exposure-efficacy relationship has been demonstrated in UC subjects in Study C13006, where higher serum vedolizumab concentrations were associated with higher efficacy.

Therefore, a vedolizumab SC dosing regimen that provides similar exposure to that from the recommended vedolizumab IV dosing regimen is predicted to provide similar efficacy and have a similar safety profile. The vedolizumab SC maintenance dosing regimen of 108 mg Q2W was selected based on modeling and simulations from the preliminary results from the single-dose phase 1 study MLN0002SC-101, where the SC bioavailability was assessed for vedolizumab SC at different dose levels. At this vedolizumab SC dose level, it is anticipated that the average serum concentration over the dosing interval at steady-state ($C_{av,ss}$) will match the recommended vedolizumab IV maintenance dosing regimen, while the steady-state trough serum concentration (C_{trough}) levels will be approximately twice the levels achieved in the vedolizumab IV Q8W regimen, but below the vedolizumab IV Q4W regimen.

A dose escalation regimen of vedolizumab SC 108 mg QW will be administered in subjects with loss of clinical response at enrollment in the current study, or who lose response or experience treatment failure during the current study. This regimen is expected to result in similar $C_{avg,ss}$ value to that of vedolizumab IV 300 mg Q4W and approximately double in comparison to vedolizumab SC 108 mg Q2W or vedolizumab IV 300 mg Q8W, while the C_{trough} is expected to be approximately 50% higher compared to vedolizumab IV 300 mg Q4W. Higher multiple doses (6 and 10 mg/kg) have been evaluated in a limited number of UC subjects in phase 2 vedolizumab IV studies (C13002 and C13004), and the exposure, including C_{trough}, achieved at these higher doses was higher than the steady-state exposure from SC 108 mg QW regimen. The safety profile at these higher doses from the phase 2 studies was consistent with Q8W and Q4W dosing, suggesting a lack of additional safety concerns at the proposed vedolizumab SC dose escalation regimen (108 mg QW). Based on the long-term vedolizumab IV safety data from the C13008 study this dose escalation regimen is expected to lead to improved efficacy without unacceptable increase in safety risk.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the product, such that the risk/benefit is no longer acceptable for subjects participating in the study.

The Data Monitoring Committee recommends the study should be suspended or terminated.

Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to 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 or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject has previously participated in Study MLN0002SC-3027 or MLN0002SC-3031, and, in the opinion of the investigator, tolerated the study drug well. Subjects who withdraw early from Study MLN0002SC-3027 or MLN0002SC-3031 must have withdrawn due to treatment failure (ie, as determined by disease worsening or need for rescue medications from Week 14) during the Maintenance Phase.
4. The subject has previously participated in Study MLN0002SC-3027 or MLN0002SC-3031, and, in the opinion of the investigator, tolerated the study drug well. Subjects who did not achieve a clinical response at Week 6 and were not randomized into the Maintenance Phase, and achieved a clinical response at Week 14 after receiving a third open-label vedolizumab IV infusion are eligible to participate.
5. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.
6. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.

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

7. Subjects with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factor must be up-to-date on colorectal cancer surveillance. Note: If enrolled, subjects should be encouraged to undergo surveillance colonoscopies as per local guidelines throughout their participation in this study.
8. Subjects with extensive colitis or pancolitis of >8 years duration or left-sided colitis of >12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of the initial Screening Visit of MLN0002SC-3027 or MLN0002SC-3031.

9. May be receiving a therapeutic dose of the following drugs provided that the dose has been stable throughout the qualifying double-blind study:
    - Oral 5-ASA compounds.
    - Oral corticosteroid therapy (prednisone or equivalent steroid at a dose ≤30 mg/day, budesonide at a dose ≤9 mg/day).
    - Probiotics (eg, Culturelle, *Saccharomyces boulardii*).
    - Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea.
    - Antibiotics used for treatment of IBD (eg, ciprofloxacin, metronidazole).
    - Azathioprine or 6-mercaptopurine, provided the subject was receiving this medication during prior participation in Study MLN0002SC-3027 or MLN0002SC-3031.
    - Methotrexate, provided the subject was receiving this medication during prior participation in Study MLN0002SC-3031.

7.2 Exclusion Criteria

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

1. The subject required surgical intervention for UC or CD during or after participation in Study MLN0002SC-3027 or MLN0002SC-3031, currently requires surgical intervention for IBD, or is anticipated to require surgical intervention for UC or CD during this study.
2. The subject has had previous exposure to approved or investigational anti-integrins (eg, natalizumab, efalizumab, etrolizumab, AMG-181) or anti-MAdCAM-1 antibodies or rituximab.
3. The subject has had hypersensitivity to any of the vedolizumab excipients.
4. Any live vaccinations within 30 days prior to vedolizumab SC administration.
5. The subject has developed a chronic or severe infection, or, any new, unstable, or uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, neurologic, oncologic, or other medical disorder during or after participation in a prior vedolizumab study that, in the opinion of the investigator, would confound the study results or compromise subject safety.
6. The subject has withdrawn from Study MLN0002SC-3027 or MLN0002SC-3031 due to a study-drug related AE.
7. The subject is unwilling or unable to self-inject, or does not have a caregiver (defined as a legal adult) to inject the study medication.
8. The subject has any history of malignancy, except for the following: (a) adequately treated nonmetastatic basal cell skin cancer; (b) squamous cell skin cancer that has been adequately

treated and that has not recurred for at least 1 year prior to enrollment; and (c) history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years prior to enrollment. Subjects with remote history of malignancy (eg, >10 years since completion of curative therapy without recurrence) will be considered based on the nature of the malignancy and the therapy received and must be discussed with the sponsor on a case-by-case basis prior to enrollment.

9. The subject has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, or demyelinating neurodegenerative disease.
10. The subject has a positive PML subjective symptom checklist prior to the administration of study drug.
11. The subject has any of the following laboratory abnormalities prior to the administration of study drug:
    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. ALT or AST >3 × the upper limit of normal (ULN).
    vi. Alkaline phosphatase >3 × ULN.
    vii. Serum creatinine >2 × ULN.
12. 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 enrollment.
13. The subject has an active psychiatric problem that, in the investigator's opinion, may interfere with compliance with study procedures.
14. The subject or caregiver is unable to attend all the study visits or comply with study procedures.
15. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 18 weeks after participating in this study; or intending to donate ova during such time period.
16. If male, the subject intends to donate sperm during the course of this study or for 18 weeks thereafter.
17. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

7.3 Excluded Medications and Treatments

- Treatments for IBD other than those specifically listed in the protocol (either approved or investigational).
- All live vaccines during study treatment and for at least 6 months after the last dose of study drug.
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use. (Note: occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc, and daily use of baby or low-dose [81-162.5 mg] aspirin for cardiovascular prophylaxis are permitted.)
- Leukocytapheresis (LCAP) (white blood apheresis) or granulocytapheresis (GCAP) (Japan only).
- Enteral nutrients (>900 kcal/day) (Japan only).

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

7.3.1 Permitted Medications and Treatments

The following medications are permitted during the study and should remain stable throughout:

- Oral and topical (rectal) 5-ASA treatment.
- Oral corticosteroids are permitted (but may not increase above the dose at Week 0) through 6 months after enrollment. Subjects must complete corticosteroid tapering within 6 months or discontinue vedolizumab SC and withdraw from the study.
- Topical (rectal) treatment with corticosteroid enemas/suppositories.
- Probiotics (eg, Culturelle, *S. boulardii*).
- Antidiarrheals for control of chronic diarrhea.
- Antibiotics used for the treatment of CD.
- Topical steroid treatment for new extraintestinal manifestations (only) of IBD (after approval by the sponsor).

Any medications used during the parent study are permitted to continue during the OLE study.

Any new medication or any increase in dose of a baseline medication required to treat new or unresolved UC or CD symptoms (other than anti-diarrheals for control of chronic diarrhea) is considered a rescue medication. Administration of a rescue medication constitutes treatment failure (ie, lack of efficacy) and the subject should be withdrawn from the study according to Section 7.5.

7.3.2 Oral Corticosteroid Dosing and Tapering

The maximum dose of oral corticosteroid for the treatment of UC or CD that may be coadministered with vedolizumab SC as a long-term regimen is 30 mg/day of prednisone (or equivalent), or 9 mg/day of budesonide. Subjects who require consistent doses higher than 30 mg/day of prednisone (or equivalent) should be withdrawn from the study. Cases in which the investigator believes the subject should stay on study must be discussed with the medical advisor or the Takeda medical monitor.

Subjects receiving oral corticosteroids will begin an oral corticosteroid tapering regimen once they either achieve clinical response or if, in the opinion of the investigator, they have demonstrated sufficient improvement in clinical signs and symptoms since participation in another vedolizumab SC study.

The recommended tapering schedule is as follows:

- For prednisone at doses >10 mg/day (or equivalent), the dose should be reduced at a rate of 5 mg per week until a 10 mg/day dose is reached.
- For prednisone at doses ≤10 mg/day (or equivalent) or once a 10 mg/day dose (or equivalent) 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.
- Investigators should strongly consider withdrawing subjects who require recurrent corticosteroid courses with an inability to taper.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

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

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

    - LFT Abnormalities.

      Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.9), if the following circumstances occur at any time during study medication treatment:

      – ALT or AST >8 × ULN, or

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

- ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
- ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

2. Significant protocol deviation. The discovery after the first dose of study medication 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. Three attempts to contact the subject must be documented (ie, 2 attempts by phone and 1 attempt by registered letter).
4. Voluntary withdrawal. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category).
5. Study termination. The sponsor, IRB, IEC, 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 9.1.1.1.
7. Lack of efficacy.
   - Treatment failure as determined by disease worsening (as defined in Section 9.3.2) or need for rescue medications (as defined in Section 7.3.1) in subjects receiving the vedolizumab SC QW regimen.
   - Need for major surgical intervention for the treatment of UC or CD.
8. Leukopenia or lymphopenia: WBC and lymphocyte counts will be monitored for all subjects. Azathioprine, 6-mercaptopurine, or methotrexate, if applicable, should be discontinued and the dose of study drug held for an absolute lymphocyte count $<0.5\times10^9$/L at any point in the study. The absolute lymphocyte count must be repeated at appropriate intervals as determined by the investigator. The next dose of study drug can be administered only if the absolute lymphocyte count is $\geq0.5\times10^9$/L. If the absolute lymphocyte count remains $<0.5\times10^9$/L, study drug should be discontinued and the subject withdrawn from the study.
9. Other.

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

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4. 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 Early Termination (ET) Visit and LTFU (Final Safety Follow-up Visit and 6 month LTFU survey). Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to all or any of the drugs defined below.

Additional reference information and administration instructions for study medication can be found in the Pharmacy Manual.

8.1.1.1 Vedolizumab Injection, for Subcutaneous Use (Vedolizumab SC)

The study sites will be supplied with the following medication in an open-label manner: vedolizumab SC 108 mg/0.68 mL in a PFS. The study medication is a liquid formulation provided in prefilled syringe with backstop and plunger rod assembled together. Each syringe will be packaged in folding box or carton.

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

8.1.1.2 Vedolizumab SC in AI

The study sites will be supplied with the following medication in an open-label manner: liquid vedolizumab SC 108 mg/0.68 mL in single-use bare glass PFS housed in an AI (PFS+AI). Each PFS+AI will be packaged in a single plastic tray with sealed lidding, within a folding box or carton.

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

8.1.1.3 Vedolizumab SC in NSD

The study sites may be supplied with the following medication in an open-label manner: liquid vedolizumab SC 108 mg/0.68 mL in single use bare glass PFS housed in the NSD with finger flange (PFS+NSD). Each PFS+NSD will be packaged in a single plastic tray with sealed lidding, within a folding box or carton.

Each sealed tray and folding box or carton will have a single-panel or multilingual booklet label that will contain but will not be limited to the following: sponsor's name and address, protocol

number, packaging job lot number, name and strength of the product, caution statement, directions for use, and storage conditions.

8.1.1.4 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following:

- Vedolizumab Injection, for Subcutaneous Use (vedolizumab SC).

8.1.1.5 Other Protocol-Specified Materials

The following supplies will also be required for study drug administration and are to be provided by the clinical study center unless otherwise indicated:

- Alcohol swabs.
- Needle sharps container (provided by sponsor).

8.1.2 Storage

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

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

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

Table 8.a Dose and Regimen

Treatment Group	Dose	Treatment Description	
A	Vedolizumab SC 108 mg	Open-label	Weeks 0-study end (Q2W)
B	Vedolizumab SC 108 mg	Open-label	Weeks 0-study end (QW)

8.1.3 Overdose

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

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

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

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

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive treatment according to the schedule allocated to each study site.

The investigator or investigator's designee will access the interactive web response system (IWRS) prior to Week 0 to register a subject as eligible. Subjects will retain their subject ID from their respective parent study (MLN0002SC-3027 or MLN0002SC-3031). The investigator or the investigator's designee will utilize the IWRS to enroll the subject into the study. The medication identification (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.

For SC injection, the recommended sites are the lower abdomen (except for the 2 inch area around the navel), the outer area of the upper arms, and the front of the thighs. The injection site should be changed for consecutive injections. Each new injection should be given at least 1 inch from a site used before.

During clinic visits, vedolizumab SC injections may be administered by the subject (or caregiver) under the supervision of a 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 during the administration and for one hour following completion of the administration.

Study medication storage, disposal and directions for use for the subject injections will be described in information provided to the subject.

For further dispensing information, please refer to the pharmacy and/or appropriate study manual.

Japan Only

Subjects who choose to switch presentation will be randomized (1:1) to PFS+NSD or PFS+AI, and randomization will be stratified by the subject's underlying disease, UC or CD. The investigator or investigator's designee will use the IWRS to confirm which presentation the subject will be randomized to.

8.3 Randomization Code Creation and Storage

This is an open-label study.

Japan Only

Randomization personnel of the sponsor or designee will generate the randomization schedule for subjects who switch to PFS+NSD or PFS+AI. An IWRS system will be used for subject randomization. All randomization information will be stored in a secured area, accessible only by authorized personnel.

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

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment (by signing bottom half of the packing list and faxing per instructions provided on the form or by recording in IWRS). If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

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

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot/medication ID/job number used to prepare each dose.
- Verifying that all containers used/assigned are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

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

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

The investigator or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. The following information will be recorded at a

minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, date and amount dispensed including initials, date and amount returned to the site by the subject, and the initials, seal, or signature of the person dispensing the drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

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.

Subjects will retain the unique subject identification number (subject number) assigned to them in their respective parent study, this subject number will be used throughout this OLE study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will be as collected in MLN0002SC-3027 or MLN0002SC-3031 (include date of birth or age or date of birth [depending on local regulations]), sex, Hispanic ethnicity, race as described by the subject, and smoking status of the subject).

Medical history will be obtained from the parent study.

Medication history information to be obtained includes any medication relevant to eligibility criteria prior to signing of informed consent. Monitoring of concomitant medications and concomitant procedures will begin at enrollment. Any medications that are ongoing at the end of the previous study and that are still present at the time of enrollment into the MLN0002SC-3030 study will be recorded in the eCRF for Study MLN0002SC-3030.

9.1.3 Physical Examination Procedure

A baseline physical examination for MLN0002SC-3030 (defined as the assessment prior to first dose of investigational drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination. Clinically significant findings will be recorded as an AE if it starts after the first dose of study drug on this study.

9.1.4 Weight and Height

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place.

9.1.5 Vital Sign Procedure

Vital signs will include body temperature, respiratory rate, blood pressure (sitting), and pulse (beats per minute).

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

On dosing days, vital signs are taken predose.

9.1.6 Primary Efficacy Measurement

UC disease activity will be followed throughout this study using the partial Mayo score, a standardized measure for UC trials that includes 3 of the 4 components of the complete Mayo score [35]. CD disease activity will be followed throughout this study using the HBI, a standardized measure for CD trials that has previously been demonstrated to correlate highly with CDAI [36]. [redacted]

9.1.6.1 Diary Completion and Review

Diary entries will be made daily by subjects entering from the parent study and will be used for calculating the partial Mayo score. During eligibility assessment, subjects will be re-instructed on how to appropriately complete the daily diary. The symptoms of UC must be recorded in the diary throughout the study. Diary entries will be made daily by the subject through a validated electronic system. Entries should be reviewed and monitored by the study staff.

9.1.6.2 Collection of Subject-Reported Components of HBI Score

Subject-reported components of the HBI score will be collected at the site during clinic visits and recorded into an electronic device by the subject.

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.8 Documentation of Concurrent Medical Conditions

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

9.1.9 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures at the time points specified in the Schedule of Study Procedures. The maximum volume of blood at any single visit is approximately 22 mL, and the approximate total volume of blood for the study per year of participation is 100 mL.

Details of these procedures and required safety monitoring will be given in the laboratory manual.

Clinical laboratory tests to be performed in this study are summarized in Table 9.a.

Refer to the Schedule of Study Procedures in Appendix A for timing of all assessments.

Table 9.a Clinical Laboratory Test

Hematology	Serum Chemistry	Urinalysis
RBC	ALT	Bilirubin
WBC w/ differential	Albumin	Blood
Hemoglobin	Alkaline phosphatase	Glucose
Hematocrit	Amylase	Ketones
Platelets	Lipase	Leukocyte esterase
PT/INR	AST	Nitrite
	Total and direct bilirubin	pH
	Total protein	Protein
	Creatinine	Specific Gravity
	Blood urea nitrogen	
	Creatine kinase	Microscopic (to be obtained in the event of positive leukocyte esterase or blood, will include WBCs, RBCs, and cast[s])
	GGT	
	Potassium	
	Sodium	
	Calcium	
	Chloride	
	Bicarbonate	
	Magnesium	
	Phosphorus	
	Uric Acid	
	Glucose	
Other:		
[redacted]	Beta hCG and Urine Pregnancy hCG (female subjects of childbearing potential) FSH (a)	

FSH=follicle-stimulating hormone, GGT=γ-Glutamyl transferase, HBsAg=hepatitis B surface antigen, hCG=human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cell.
(a) FSH level will be obtained for female subjects prior to Week 0 if they are postmenopausal by history (ie, last regular menstrual cycle >1 years) and not surgically sterile. The FSH results must be >40 IU/L for the subject to be permitted not to use contraception

Central laboratories will perform laboratory tests for hematology, serum chemistries, and urinalysis as well as specialty testing outlined above. The results of safety laboratory tests will be

returned to the investigator, who is responsible for reviewing and filing these results. Refer to the schedule of events for timing of all assessments.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

(Please refer to Section 7.4 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

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

9.1.10 Contraception and Pregnancy Avoidance Procedure

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

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception will be:

Barrier methods (each time the subject has intercourse):

- Male condom PLUS spermicide.
- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.

Intrauterine devices (IUDs):

- Copper T PLUS condom or spermicide.
- Progesterone T PLUS condom or spermicide.

Hormonal contraceptives:

- Implants.
- Hormone shot/injection.
- Combined pill.
- Minipill.
- Patch.
- Vaginal ring PLUS male condom and spermicide.

Subjects will be provided with information on acceptable 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.

During the course of the study, subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A).

All female subjects of child bearing potential must have a serum pregnancy test at the ET/Final Safety Visit. A urine pregnancy test will be completed for all females of child bearing potential on a monthly basis prior to administration of study drug.

9.1.11 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn, and any sponsor-supplied drug should be immediately discontinued and returned to the study site. In addition, any pregnancies in the partner of a male subject during the study or for 18 weeks after the last dose, should also be recorded following authorization from the subject's partner.

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

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

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

9.1.12 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

Any findings from ECGs collected after study drug administration at Week 0 will be captured as AEs if, in the opinion of the investigator, there has been a clinically significant change from Baseline.

Subjects will be supine and will have rested for 5 or more minutes before any ECG is recorded. Tracings will include subject number and initials and the date and time of recording and all other subject identifiers will be removed or obscured.

9.1.13 [redacted]

[redacted]

9.1.14 [redacted]

[redacted]

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 of the MLN0002SC-3027 or MLN0002SC-3031 study and at any point in the MLN0002SC-3030 study when a subject becomes symptomatic, including worsening of disease.

9.1.16 [redacted]

[redacted]

9.1.17 PML Checklist

Staff will administer the subjective PML checklist during Week 0 to exclude subjects with positive responses from enrolling into the study. The PML subjective checklist will be administered in person prior to dosing at visits occurring in the clinic. The PML subjective checklist will be

administered over the telephone prior to dosing when the subject is injecting vedolizumab SC outside of the clinic.

Any subjects reporting signs or symptoms of PML will be told to withhold the respective dosing and will undergo physician-administered objective testing and may be referred to a neurologist for a full evaluation, as described in the RAMP Algorithm referenced in Section 11.1.1. The symptoms from a positive PML checklist will be recorded as an AE in the eCRF.

Additional information and tools for the RAMP can be found in the appropriate Study Manual.

9.1.18 Patient Reported Outcomes Measures

Subjects will complete the IBDQ and EQ-5D health-related quality of life (HRQOL) questionnaires at the time points specified in the schedule of events (Appendix A). Subjects will also complete the WPAI-UC or WPAI-CD to assess the impact of disease on loss of work productivity and activity impairment.

9.1.18.1 Inflammatory Bowel Disease Questionnaire

The IBDQ is a valid and reliable [37] instrument used to assess quality of life in adult subjects with IBD. It includes 32 questions on 4 domains of HRQOL: Bowel Systems (10 items), Emotional Function (12 items), Social Function (5 items), and Systemic Function (5 items). Subjects are asked to recall symptoms and quality of life from the last 2 weeks and rate each item on a 7-point Likert scale (higher scores equate to higher quality of life). A total IBDQ score is calculated by summing the scores from each domain; the total IBDQ score ranges from 32 to 224.

9.1.18.2 EQ-5D Questionnaire

The EQ-5D questionnaire, developed by the 'EuroQol Research Foundation' is a simple, valid, and reliable [38] instrument used to measure general HRQOL in subjects and includes 5 domain items - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Subjects choose the level of health problems they currently have on each item as "None", "Moderate", or "Extreme" and are scored a 1, 2, or 3, respectively. A composite EQ-5D score can be calculated from the individual scores to assess overall HRQOL. The EQ-5D visual analog score (VAS) score is a self-assigned rating of overall health using a 20 cm visual, vertical scale, with a score of 0 as the worst and 100 as best possible health. The EQ-5D index score and EQ-5D VAS score have been shown in many studies to be valid and reliable instruments for measuring HRQOL in patients with GI diseases.

9.1.18.3 Work Productivity and Activity Impairment-UC or CD

The WPAI questionnaire is a valid and reliable [39] 6-item instrument that consists of 4 metrics: absenteeism (the percentage of work time missed because of one's health in the past 7 days), presenteeism (the percentage of impairment experienced while at work in the past 7 days because of one's health), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of

impairment in daily activities because of one's health in the past 7 days). The sum of specific health problem impairment and impairment due to other health reasons is equal to impairment due to all health reasons. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes. WPAI-UC is the UC specific disease version of the questionnaire. WPAI-CD is the CD specific disease version of the questionnaire.

9.1.19 Eligibility Assessment

Subjects will be assessed for eligibility during the ET/Week 52 visit (including the Week 14 responders) for the MLN0002SC-3027 or MLN0002SC-3031 study. If eligible they will undertake the informed consent process. The Week 0 visit first dose of vedolizumab SC should occur in accordance with Section 6.1.

9.1.20 Documentation of Enrollment (Week 0) Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible at the Week 0 Visit, the investigator should complete the eCRF. The IWRS should be contacted as a notification of enrollment failure.

The primary reason for enrollment failure is recorded in the eCRF using the following categories:

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

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

9.1.21 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance at Week 0 into the Treatment Period.

If the subject is found to be not eligible for the Treatment Period, the investigator should record the primary reason for failure on the applicable eCRF. Subject eligibility will not be reassessed.

9.1.22 Procedure for Switching to PFS+NSD and PFS+AI

Subjects (not including those in Japan) will be switched from administering vedolizumab SC in PFS to administration using PFS+AI once the PFS+AI presentation is available. Subjects will

receive training on how to use PFS+AI before starting self-injection at home. An additional clinic visit for training can be arranged as needed. After switching to PFS+AI, subjects will continue with all procedures as per the study schedule during the remaining length of the OLE study.

If PFS+AI is not available at the site for any reason, subjects may, at the discretion of the sponsor, be provided PFS+NSD or PFS for injection. Subjects may be switched back to PFS or to PFS+NSD only at the sponsor's request if any concern or issue is identified with or PFS+AI. Additional training on devices will be provided, if needed.

Subjects will receive training prior to receiving vedolizumab SC PFS+AI for self-administration at home. An additional clinic visit for training can be arranged as needed.

The following information will be recorded:

- Vedolizumab SC presentation used at each dosing (PFS, PFS+AI).
- Date and reason for discontinuation of self-injection (if relevant).

Japan Only

In Japan, subjects can switch to PFS+NSD or PFS+AI at any scheduled or unscheduled visit beginning at the Week 16 visit. Informed consent must be obtained before the switch and any related procedures. Only subjects who opt to switch will be randomized. Randomization will be (1:1) to PFS+NSD or PFS+AI with stratification by disease (UC or CD).

Subjects will not be permitted to switch between PFS+NSD and PFS+AI. Subjects may be switched back to PFS if a safety concern, lack of self-injection capability, or other issue including but not limited to lack of availability of the device is identified with PFS+NSD or PFS+AI.

For subjects that switch to the PFS+NSD or PFS+AI, the amended procedures will be applied as follows:

- Vedolizumab SC injections should be performed by subjects themselves, if the subject is considered capable of self-injection in the opinion of the investigator.
- Subjects must receive training by the investigator or subinvestigators at the site on how to self-inject with the PFS+NSD or PFS+AI and how to take actions for injection-associated risks. Subjects must complete at least 2 onsite training sessions before starting self-injection at home. Additional clinic visits for the training sessions may be required. Criteria for switch to self-injection at home and discontinuation of self-injection with PFS+NSD or PFS+AI are described in Table 9.b.

[redacted]

- Additional items related to use of PFS+NSD or PFS+AI must be recorded in the eCRF.
  - Presentation used at each dosing (PFS or PFS+NSD or PFS+AI).

- Injection conditions (self-injection at home/at site, or injection by investigator or subinvestigator at site).
- Date of discontinuation of self-injection with PFS+NSD or PFS+AI, reason for the discontinuation, and related comments.

Table 9.b Criteria for Switch to Self-Injection of Vedolizumab SC via PFS+NSD or PFS+AI at Home and Discontinuation of Self-Injection of Vedolizumab SC via PFS+NSD or PFS+AI

Criteria for switching to self-injection at home	Self-injection at home will be permitted if the subject satisfies all of the following criteria: • Subjects who have completed training at least 2 visits with the investigator or subinvestigator at site on how to use PFS+NSD or PFS+AI and how to take actions for injection-associated risks. If the investigator or subinvestigator find any problem in self-injections with PFS+NSD or PFS+AI during observation, the training should be repeated as needed. • Subjects who are confirmed capable of self-injection with vedolizumab SC via PFS+NSD or PFS+AI (ie, self-injection can be performed without any problem, and the appropriate action against injection-associated risks) by investigator or subinvestigator.
Criteria for discontinuation of self-injection	Self-injection with vedolizumab SC via PFS+NSD or PFS+AI should be discontinued if any of the following criteria is met: • Subject is withdrawn from the OLE study for any reason listed in Section 7.4. • Lack of self-injection capability using PFS+NSD or PFS+AI despite multiple retrainings. • Per sponsor's request if any safety concerns with any of the presentations should arise.

9.2 Monitoring Subject Treatment Compliance

If a subject is persistently noncompliant with the study medication, it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

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 Study Entrance

Study entrance to the Treatment Period 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 enrollment failures is provided in Section 9.1.20.

Subjects entering this OLE study must have participated in the MLN0002SC-3027 or MLN0002SC-3031 study:

- Subjects with UC or CD who completed the Maintenance Phase (Week 52 assessment) will receive vedolizumab SC 108 mg Q2W.
- Subjects with UC or CD who withdrew early from the Maintenance Phase (at Week 14 onwards) due to disease worsening or need for rescue medications will receive vedolizumab SC 108 mg QW.
- Subjects with UC and CD who did not achieve a clinical response at Week 6 in the parent study but who did achieve a clinical response at Week 14 of the parent study after having received a third vedolizumab IV infusion at Week 6 in the parent study will receive vedolizumab SC 108 mg Q2W.

9.3.2 Final Visit or Early Termination

It is anticipated that the duration of vedolizumab SC treatment will vary by subject based on continued benefit, but will be until vedolizumab SC is available in the subject's country commercially or through other access programs, or if the subject withdraws from the study, or the sponsor decides to close the study.

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

Subjects with disease worsening due to lack of efficacy will be withdrawn.

Disease worsening is defined as:

- In UC subjects while participating in:
  - Study MLN0002SC-3027: An increase in partial Mayo score of ≥3 points on 2 consecutive visits from the Week 6 (of MLN0002SC-3027 study) value (or an increase to 9 points on 2 consecutive visits if the Week 6 value >6) and a minimum partial Mayo score of ≥5.
  - Study MLN0002SC-3030: An increase in partial Mayo score ≥3 points on 2 consecutive visits from the Week 0 (of MLN0002SC-3030 study) value (or an increase to 9 points on 2 consecutive visits if the Week 0 value >6) and a minimum partial Mayo score of ≥5.

- In CD subjects while participating in:
  - Study MLN0002SC-3031: A ≥100-point increase in CDAI score on 2 consecutive visits from the Week 6 (of MLN0002SC-3031 study) value at any study visit and a minimum CDAI score of 220 points.
  - Study MLN0002SC-3030: A ≥4-point increase in HBI score on 2 consecutive visits from the Week 0 (of MLN0002SC-3030 study) value and a minimum HBI score of 7 points.

At any time during Study MLN0002SC-3030, subjects who experience treatment failure (ie, disease worsening, requirement for rescue medications):

- While receiving vedolizumab 108 mg Q2W during this OLE study: will undergo dose escalation and continue to receive vedolizumab 108 mg QW.
- While receiving vedolizumab 108 mg QW during this OLE study: will be withdrawn from the study.

Subjects who have AEs related to study drug that lead to drug discontinuation or require a surgical intervention for their UC or CD will be withdrawn.

9.3.3 Final Safety Follow-up Visit

After the final dose of vedolizumab SC on the study, subjects will complete a Final Safety Follow-up visit 18 weeks after the last dose.

9.3.4 Post Study 6-Month Long-Term Follow-Up Survey

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

9.3.5 Unscheduled Visits Due to Disease Exacerbation

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

- Physical examination.
- Vital signs assessment.
- Diary review.
- Collection of concomitant medications and procedures.
- 12-lead ECG.
- Collection of AEs and SAEs.
- Clinical chemistry and hematology, coagulation, urinalysis and pregnancy test (as indicated).
- Partial Mayo score calculation.

- HBI.
- [redacted]
- [redacted]
- *C. difficile*, if indicated.
- Escalation to QW dosing and PML checklist, if applicable.

There is no minimum time for repeat evaluation by unscheduled visit in order to determine if a subject meets the criteria for disease worsening. In general, however, enough time should be provided for clinically meaningful change to occur.

9.3.6 Poststudy Care

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

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

In unavoidable circumstances, in particular a pandemic (eg, COVID-19 or other future similar unexpected public health concerns), 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 participants or study sites that are affected by a pandemic (eg, COVID-19 or other future similar unexpected public health concerns) that require physical distancing that may result in subjects missing their visits. This guidance is aligned with the current guidance from global health authorities on the conduct of clinical studies during the COVID-19 pandemic.

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

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

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

- All attempts should be made to perform the assessments with the subject present at the site using the visit windows. Exceptions may be granted for alternative approaches to study procedures and data collection through approval by the sponsor or designee. Such instances must be documented in the study records and may include the following:

  - Sites impacted by a pandemic (eg, COVID-19) must contact the sponsor or designee to discuss individual subject and site circumstances to obtain approval for use of alternative approaches to study procedures and data collection.
  - Sites may seek approval from the Medical Monitor 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 participants and site personnel for subjects to continue. In evaluating such requests, the sponsor or designee will give the highest priority to the safety and welfare of the subjects. Subjects must be willing and able to continue taking study medication and remain compliant with the protocol.

- Informed Consent Procedure: If necessary and if required locally, informed consent from a study participant may be obtained via verbal consent when these individuals are unable to travel to the site. Informed consent forms will be signed once the subject can return in person to the study site.
- Clinic Visits: For clinic visits (other than the Final Visit/ET Visit and the Final Safety Follow-up Visit), alternative methods for conducting subject visits (eg, video conferencing, telephone visits) may be used with prior approval by the sponsor or designee (ie, telemedicine visit):
  - When approval is given for a clinic visit to be conducted using an alternative approach, a study site physician will speak directly with the subject by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status.
  - Assessments: During visits using an alternative method, the study site physician or other qualified site personnel should contact the subject and conduct the following assessments within specified visit window timeframes: AE/SAE collection, documentation of concomitant medication and procedures, diary review, administration of the subjective PML checklist, subject assessment of disease activity based on subject-reported symptoms, and PRO assessments (IBDQ, EQ-5D, and WPAI). Sites may record the scores of the IBDQ, EQ-5D, and WPAI assessments on behalf of the subject, with the subject's agreement in the event of a telemedicine visit.
  - Primary Efficacy Measurement: For subjects with CD, during telemedicine visits that are conducted with prior approval by the sponsor or designee due to unavoidable circumstances related to a pandemic (eg, COVID-19), sites may record subject-reported components of the HBI score on behalf of the subject during the telemedicine visit, with the subject's agreement. In such situations, site personnel would not be able to access any data provided by the subject at any other visit. For subjects with UC, subject-reported components of the partial Mayo score should be recorded in the daily diary per protocol. For all subjects, the investigator's assessment of disease activity should still be performed based on subject-reported symptoms and recorded in the source documents even if a physical examination cannot be performed.

- Collection of Clinical Laboratory Samples: Safety laboratory assessments (ie, clinical chemistry and hematology) should be conducted at least every 24 weeks. If a subject is unable to visit the study site due to a pandemic (eg, COVID-19), sites may elect to use local laboratories if it is feasible for the subject to visit a local laboratory sooner than the study site for sample collection. Local laboratory assessments should include clinical chemistry and hematology, as specified in Table 9.a, and results should be communicated to the Medical Monitor and used to ensure subject safety. Stool samples and collection of samples for FSH, [redacted] are not required when local laboratories are used; however, sampling for these assessments will be resumed upon the subject's subsequent visit to the site. Female subjects of childbearing potential will continue to complete at-home urine pregnancy tests on a monthly basis prior to administration of study drug.
- Protocol Deviations: Any deviations from the protocol-specified procedures due to a pandemic (eg, COVID-19 or other similar pandemic) will be recorded as related to a pandemic (eg, COVID-19).

- Final Visit/ET Visit and Final Safety Follow-up Visit: The Final Visit/ET Visit and the Final Safety Follow-up Visit should be performed with the subject present at the study site. If the visit cannot be conducted onsite within the visit window, sites may conduct final visit procedures remotely as is feasible, including using local laboratories for assessment of clinical chemistry and hematology (as specified in Table 9.a). Assessments that cannot be completed during the protocol-specified window will be recorded as a protocol deviation, and such deviations will be recorded in the study records as related to a pandemic (eg, COVID-19 or other similar pandemic).
- SC Injection Training and Monitoring of Hypersensitivity Reactions: See Section 6.1 for subject/caregiver training upon study entry of proper SC injection and management of hypersensitivity reactions potentially associated with an SC injection. See Section 9.1.17 for procedures related to the PML checklist and Section 11.1.1 for training procedures of site personnel and subjects in recognizing signs and symptoms of PML. See Section 10.2 for procedures for collecting and reporting AEs, SAEs, and abnormal LFTs.
- For all SC dosing occurring outside of the clinic, subjects will receive a phone call from study staff within 24 hours prior to every injection for these scheduled doses to administer the PML subjective checklist and inquire about general health status and experience with prior injection (see Section 6.1). This telephone visit should occur before every dose occurring outside of the clinic, regardless of any alternative procedures implemented due to a pandemic (eg, COVID-19).
- In cases of a positive PML checklist or 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 a pandemic (eg, COVID-19), the site should contact the Medical Monitor.

- Alternative Study Medication Delivery via DTP Shipment: During a pandemic (eg, COVID), alternative study medication delivery to subjects may be necessary to provide study medication if an in-person visit to the study site is not feasible. In this situation, study medication (no more than an 8-week supply) may be shipped directly from study sites to the subject's residence by a contracted logistics provider or distributor (DTP shipment) in compliance with national laws or temporary national emergency measures and with sponsor standard operating procedures. Details of the process are provided in the pharmacy manual.
- 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 a pandemic (eg, COVID-19), this must be specified as the reason for subject withdrawal in the eCRF.
- AEs of COVID-19–related disease and COVID-19 pneumonia are now included as medically significant AEs (see Table 10.a).

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

9.4 Biological Sample Retention and Destruction

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

Samples will be stored for no longer than 15 years after completion of the study. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Takeda.

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

Subjects who consented and provided pharmacogenomic samples in the prior study can withdraw their consent and request disposal of their stored sample at any time. Notify sponsor of consent withdrawal.

10.0 PRETREATMENT EVENTS (PTE) ADVERSE EVENTS (AE) AND PRODUCT COMPLAINTS (PC)

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation. For this study that is the time period between ET/Week 52 of the parent study and Week 0 of this study.

10.1.2 AEs

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

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

In addition, drug-device AEs related to quality or malfunction will be collected.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Diagnoses vs signs and symptoms:

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

Laboratory values and ECG findings:

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

Pre-existing conditions:

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

Worsening of PTEs or AEs:

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

Changes in severity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.

6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
COVID-19–related disease	Neuroleptic malignant syndrome / malignant hyperthermia
COVID-19 pneumonia	Spontaneous abortion / stillbirth and fetal death

COVID-19=coronavirus disease 2019.

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.2.3).

10.1.5 Special Interest AEs

A special interest AE (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 Severity of PTEs and AEs

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

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

10.1.7 Causality of AEs

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

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

10.1.8 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 physician.

10.1.10 Stop Date

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

10.1.11 Frequency

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

10.1.12 Action Concerning Study Medication

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

10.1.13 Outcome

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

10.1.14 Product Complaints

A product complaint (PC) is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product and/or presentation (eg, PFS, PFS+NSD, or PFS+AI).

An investigator who is made aware of or identifies a potential PC should immediately report the event to Takeda in accordance with the contact list provided to the site. Whenever possible, the associated product should be maintained in accordance with the instructions pending further guidance from a Takeda representative. Refer to the appropriate study manual provided separately for additional information (depending on local regulations).

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

- Start of AE collection: AEs must be collected from start of study medication administration (informed consent).
- End of AE collection: AEs must be collected for 18 weeks following the last dose of study medication.

Collection of AEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Week 0) or until enrollment failure. For subjects who discontinue prior to study medication 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 medication (Week 0). Routine collection of AEs will continue until 18 weeks post last dose of medication.

10.2.1.2 AE Reporting

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

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

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

Several quality of life (QOL) instruments will be used in this study (eg, IBDQ, EQ-5D, WPAI-UC or WPAI-CD). They will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the subject for medical evaluation should be undertaken.

Through this follow-up, if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.1.3 Adverse Event Collection Involving Medically Anticipated Clinical Events

UC and CD are 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 or HBI respectively.

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

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

10.2.1.4 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 eCRF or an SAE Form. The Form should be completed and reported to SAE reporting contact in Section 1.1 within 24 hours.

Hypersensitivity Reactions (including injection site reactions).

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

During clinic visits, vedolizumab SC should be administered in the presence of a health care professional 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 during the administration and for one hour following completion of the administration.

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 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 (eg, shortness of breath, wheezing, stridor, angioedema, life-threatening change in vital signs, severe injection 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 injection-related reactions should be discussed with the Medical Monitor.

Serious Infection

Subjects will be monitored for signs and symptoms of infection and for lymphopenia during the study. Subjects with signs and symptoms suggestive of infections, including GI infections, will be treated as clinically indicated. Interventions may include antibiotic treatment, if appropriate and/or discontinuation of concomitant immunomodulators. Blood, sputum, urine, and/or stool cultures should be obtained as appropriate for the detection and diagnosis of infection. Withholding or terminating study drug administration may be considered as described in Section 7.4.

Malignancy

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

Other

Other special interest AEs include liver injury and PML, which are discussed in Sections 10.2.3 and 11.1.1 respectively.

10.2.2 Collection and Reporting of SAEs

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

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

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

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

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

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

*Note: For Japanese sites, the investigator should report the detailed paper SAE report provided by sponsor or by the institution without delay after notification of initial information. Additional detailed follow-up data surrounding the SAE that becomes available following the initial report should be communicated through the same channels as outlined above.

10.2.3 Reporting of Abnormal Liver Function Tests

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

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

10.3 Follow-up of SAEs

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

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

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

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

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

11.0 STUDY-SPECIFIC COMMITTEES

A data safety monitoring board (DSMB), independent from the sponsor, will be established to review safety data from this study on a regular basis and make appropriate recommendations regarding the safe conduct of the study.

A detailed charter will outline all activities of the DSMB (eg, type of data reviewed, frequency of meetings and location of meetings). The DSMB will be closed at the time of marketing approval.

11.1 Adjudication Committee

A PML Independent Adjudication Committee (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.

11.1.1 Risk Minimization Action Plan for PML (RAMP Program)

To address the theoretical risk of the development of PML in subjects treated with vedolizumab, the sponsor, with input from renowned PML experts, has developed a RAMP for PML. The complete description of the RAMP program, including materials and instructions for its implementation and monitoring, is included in the appropriate Study Manual.

The RAMP is focused on early clinical detection and management of that specific safety risk, including the discontinuation of study drug, if applicable. Subjects are assessed for signs and symptoms of PML prior to the administration of each dose of study drug using a PML subjective symptom checklist. Subjects with a positive PML subjective symptom checklist at any time after enrollment in a vedolizumab clinical study will be evaluated according to a prespecified algorithm (the PML Case Evaluation Algorithm). The respective dose of study drug will be withheld until the evaluation is complete and results are available. Subsequent doses of study will be administered only if the possibility of PML is definitively excluded, as described in the RAMP algorithm. An IAC has been stabled as part of the RAMP program to review new neurological signs and symptoms potentially consistent with PML, and will provide input regarding subject evaluation and management as defined in the IAC charter.

To ensure success of the RAMP program, site personnel will be trained to recognize the features of PML, and subjects will be trained to report specific neurological signs and symptoms without delay. Educational materials for teaching site personnel and subjects about PML and the RAMP procedures will be distributed to all sites and are included in the appropriate Study Manual. Formal teaching and training will be performed for site personnel prior to the start of the study. Subjects will receive training and educational materials prior to receiving treatment. The informed consent form will contain specific information on the hypothetical risk of PML. Any documented case of PML will be reported as an SAE, regardless of whether hospitalization occurs.

12.0 DATA HANDLING AND RECORD KEEPING

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

12.1 Electronic CRFs

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

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

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

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

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

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

12.2 Record Retention

1. The following procedure is applied for the countries except for Japan.

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

International Council on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

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

2. The following procedure is applied for Japanese site only.

The investigator and the head of the institution agree to keep the records stipulated in Section 12.2 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, ICH E6 Section 4.9.5 requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and/or the head of the institution and sponsor.

Refer to the Clinical 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.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and 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.

A separate SAP will be created to evaluate the efficacy and safety of switching to PFS+NSD or PFS+AI in Japanese subjects.

13.1.1 Analysis Sets

Analysis of efficacy variables will be conducted in the efficacy population, defined as all enrolled subjects. To be included in a change from baseline analysis, the subject must have had a baseline measurement.

Analysis of safety variables will be conducted in the safety population, defined as all enrolled subjects who receive at least 1 dose of study medication.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Baseline and demographic information will be listed and summarized. For continuous variables, the summary will consist of descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum). For categorical variables, the summary will consist of number and percentage of subjects in each category.

13.1.3 Efficacy Analysis

Descriptive statistics, including 95% confidence intervals, will be used in analyses of partial Mayo score (subjects with UC) or HBI score (subjects with CD). The change from Baseline in partial Mayo and HBI scores will be summarized by time point, and the means will be plotted over time. The proportion of subjects who are in clinical remission and clinical response will be summarized by time point.

13.1.4 [redacted]

[redacted]

13.1.5 Other Analysis

[redacted]

13.1.6 Resource Utilization and PRO

Descriptive statistics will be used in analyses of IBDQ, EQ-5D, and WPAI-UC and WPAI-CD scores.

Changes from Baseline in IBDQ, EQ-5D, and WPAI-UC and WPAI-CD scores will be calculated and 95% confidence intervals will be provided by time point.

Time to major UC- or CD-related events (hospitalizations, surgeries and procedures) will be analyzed using Kaplan-Meier method and 95% confidence intervals will be provided.

13.1.7 Safety Analysis

Safety evaluations will be based on incidence, severity and type of AEs, PML checklist responses, vital signs, laboratory results and ECGs. Descriptive statistics will be calculated. Safety analyses will be performed by UC subject population (overall and separately for subjects who received vedolizumab SC and subjects who received vedolizumab IV in the Maintenance Phase of Study MLN0002SC-3027) and CD subject population.

The number and percentage of subjects with TEAEs (defined as any AEs, regardless of relationship to study drug), AESIs (ie, serious infections, PML, malignancies, liver injury, injection site reactions), and SAEs which occur on or after the first dose date and up to 18 weeks after the last dose date of the study drug will be summarized by MedDRA system organ class, high level term, and preferred term overall, by severity, and by relationship to study drug. Separate summaries will also be generated for treatment-related AEs overall and by severity. Exposure

adjusted AEs will also be presented. Change from Baseline in clinical laboratory tests and vital signs will be summarized. Subjects with markedly abnormal values for laboratory tests and vital signs will be tabulated.

13.1.8 Interim Analysis

Interim analyses and reports will be done to support regulatory filings and updates.

13.2 Determination of Sample Size

The current estimate is that approximately 692 subjects: 169 UC and 348 CD subjects who will have been randomized into the Maintenance Phase of Study MLN0002SC-3027 or MLN0002SC-3031; and approximately 73 UC and 102 CD subjects who will have achieved a clinical response at Week 14 after the third vedolizumab IV infusion after not having achieved a clinical response at Week 6 will enter this study.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

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

The procedure below applies to Japanese sites only.

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

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

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

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific enrollment activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug and notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including pre-enrollment may occur.

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

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

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

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

15.4.2 Clinical Trial Registration

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

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

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

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

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Appendix A Schedule of Study Procedures

QW Dosing

STUDY PROCEDURES	Eligibility Assessment (b)	Treatment Weeks (+/- 3 days) (a)													
		Wk 0 (c) CLINIC	Wk 1 CLINIC	Wk 2 (d)	Wk 3 (d)	Wk 4 CLINIC	Wk 5, 6, 7 (d)	Wk 8 CLINIC	Wk 9 to 15 (d)	Wk 16 CLINIC (e)	Telephone Visits From Wk 16 (d)	Visits Every 8 Weeks From Wk 16 and Every 24 Weeks After Wk 72 CLINIC (e)	Unscheduled Visit (a,e,f)	Final Visit/ET (g) CLINIC	Final Safety Follow-up Visit (h) CLINIC
Informed consent	X														
Demographics	(P)														
Tobacco use	(P)														
Medical history (i)	(P)														
Prior therapies	(P)														
UC/CD disease history	(P)														
Physical examination (j)	(P)	X	X			X		X		X		X	X	X	X
Vital signs, weight (k)		X	X			X		X		X		X	X	X	X
PML checklist (l)	(P)	X	X	X	X	X	X	X	X	X	X	X		X	X
PML wallet card		X													X
Diary instruction		X													
Diary review			X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications (m)	(P)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant procedures (m)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
WPAI-UC/WPAI-CD (n)	(P)											X			
PRO (IBDQ, EQ-5D) (n)	(P)											X			
12-lead ECG	(P)												X	X	
AE/SAE assessment (o)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject assessment of disease activity (p)		X	X			X		X		X		X	X		
Dosing (q)		X	X	X	X	X	X	X	X	X	X	X			
Clinical chemistry	(P)		X			X		X		X		X	X	X	X
Hematology	(P)		X			X		X		X		X	X	X	X

Footnotes are on last table page.

Appendix A Schedule of Study Procedures: QW Dosing (continued)

STUDY PROCEDURES	Eligibility assessment (b)	Treatment Weeks (+/- 3 days) (a)													
		Wk 0 (c) CLINIC	Wk 1 CLINIC	Wk 2 (d)	Wk 3 (d)	Wk 4 CLINIC	Wk 5, 6, 7 (d)	Wk 8 CLINIC	Wk 9 to 15 (d)	Wk 16 CLINIC (e)	Telephone Visits From Wk 16 (d)	Visits Every 8 Weeks From Wk 16 and Every 24 Weeks After Wk 72 CLINIC (e)	Unscheduled Visit (a,e,f)	Final Visit/ET (g) CLINIC	Final Safety Follow-up Visit (h) CLINIC
Coagulation	(P)												X	X	
Urinalysis	(P)												X	X	
Pregnancy test (r)	X (s)	X				X		X		X	X	X	X	X	X
FSH	(P)														
[redacted]															
Stool sample (w)												X (t)	X (w)		

Footnotes:
Note: Day = day after the last dose.
(P) = obtained from previous study h=hours, Wk=week.
(a) Subjects (not including those in Japan) will switch to PFS+AI at any scheduled or unscheduled visit when they become available at the site. An additional visit for training of self-injection can be set as needed. For sites not able to conduct onsite visits due to a pandemic (eg, COVID-19 or other similar pandemic), alternative methods for conducting visits (eg, video conferencing, telephone visits) may be used with prior approval by the sponsor or designee. Safety laboratory assessments (ie, clinical chemistry and hematology) should be conducted at least every 24 weeks. If a clinic visit must be conducted via alternative methods due to a pandemic (eg, COVID-19), safety laboratory assessments may be done using local laboratories if it is feasible for the subject to visit a local laboratory sooner than the study site for sample collection. See Section 9.3.7 for guidance on alternative methods for conducting study procedures due to a pandemic.
(b) Subjects eligibility for OLE will be assessed at ET/Week 52 of the previous study (MLN0002SC-3027 or MLN0002SC-3031), or at the relevant visit for Week 14 responders. If the subject is deemed eligible they will undertake informed consent for MLN0002SC-3030. Week 0 dosing will occur in accordance with Section 6.1 of this protocol.
(c) The first 2 doses will be administered in the clinic. For all subjects, clinic visits will be at Week 0, 1, 4 and 8 and then every 8 weeks until at least Week 72 or the next visit that is a multiple of 24 (eg, Week 96, 120, 144, etc), and then every 24 weeks thereafter.
(d) Telephone visit: subjects will be contacted via telephone prior to dosing outside of the clinic every week.
(e) *Japan only:* subjects can switch to PFS+NSD or PFS+AI at any scheduled or unscheduled visit beginning from the Week 16 visit. An additional visit for training of self-injection (eg, 1 week after the switch) can be set as needed.
(f) Subjects seen at an unscheduled visit for disease exacerbation or SAE will complete the Unscheduled Visit assessments.
(g) Final Visit/ET: The duration of vedolizumab SC treatment will vary by subject based on continued benefit, but will be until vedolizumab SC is available in the subject's country commercially or through other access programs.

(h) Final Safety Follow-up Visit: Subjects will return 18 weeks after the last dose of vedolizumab SC for final safety assessments.
(i) Including reassessment of female reproductive status.
(j) A physical examination will be done at Week 0 if Week 0 is not the same day as ET/Week 52 of the parent study. Physical examinations will then be performed at Weeks 1, 4, 8, 16 and every 8 weeks until at least Week 72 or the next visit that is a multiple of 24 (eg, Week 96, 120, 144, etc), and then every 24 weeks thereafter. Clinically significant findings will be recorded as an AE if it starts after the first dose of study drug on this study.
(k) Vital signs will also be measured on dosing days prior to dosing in the clinic. Height may be taken from the parent study.
(l) The PML checklist will be administered in person at dosing occurring in the clinic during scheduled visits. The PML subjective checklist will be administered over the phone when subject is injecting outside of the clinic.
(m) Monitoring of concomitant medications and concomitant procedures will begin at enrollment. Any medications that are ongoing at the end of the parent study and that are still present at the time of enrollment into the MLN0002SC-3030 study will be recorded in the eCRF for Study MLN0002SC-3030.
(n) WPAI-UC/WPAI-CD and PRO (IBDQ, EQ-5D): To be performed at Week 24 and every 24 weeks thereafter while on study.
(o) Collection of AEs will begin following the signing of the informed consent and will continue through to Final Safety Visit. Collection of all SAEs starts at enrollment and will continue through to Final Safety Visit.
(p) Disease activity is assessed by partial Mayo score for UC subjects and by HBI for CD subjects in this study and is recorded at the clinic visits.
(q) Dosing in this study (Week 0) will occur no more than 4 weeks after the last dose of study drug for completers/ET in Study MLN0002SC-3027 or MLN0002SC-3031. For Week 14 responders from the parent study, Week 0 will occur no more than 1 week (±7 days) from Week 14 in Study MLN0002SC-3027 or MLN0002SC-3031. From Week 16, continue QW dosing. Subjects will return to the clinic every 8 weeks to receive an 8-week supply of vedolizumab SC for administration at home.
(r) Pregnancy test: All females of child bearing potential must have a serum pregnancy test at the ET/Final Safety Visit. A urine pregnancy test will be completed for all females of child bearing potential prior to each dose of study drug injected during clinic visits and monthly prior to home dosing.
(s) For Week 14 responders from the parent study, a serum pregnancy test will be performed during the eligibility assessments.

[redacted]

(w) A stool sample for culture, ova and parasite evaluation, and *C difficile* assay will be obtained at any time point during the study when a subject becomes symptomatic, including worsening or return of disease activity (if indicated).

Appendix A Schedule of Study Procedures: Q2W Dosing

STUDY PROCEDURES	Eligibility Assessment (b)	Treatment Weeks (+/- 1 week) (a) Wk 0 (c) CLINIC	Wk 2 CLINIC	Wk 4 CLINIC	Wk 6 (d)	Wk 8 CLINIC	Wk 10, 12, 14 (d)	Wk 16 CLINIC (e)	Telephone Visits From Wk 16 (d)	Visits Every 8 Weeks From Wk 16 and Every 24 Weeks After Wk 72 CLINIC (e)	Unscheduled Visit (a,e,f)	Final Visit/ET (g) CLINIC	Final Safety Follow-up (h) CLINIC
Informed consent	X												
Demographics	(P)												
Tobacco use	(P)												
Medical history (i)	(P)												
Prior therapies	(P)												
UC/CD disease history	(P)												
Physical examination (j)	(P)	X	X	X		X		X		X	X	X	X
Vital signs, weight (k)		X	X	X		X		X		X	X	X	X
PML checklist (l)	(P)	X	X	X	X	X	X	X	X	X	X	X	X
PML wallet card		X											X
Diary instruction		X											
Diary review			X	X	X	X	X	X	X	X	X	X	
Concomitant medications (m)	(P)	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant procedures (m)		X	X	X	X	X	X	X	X	X	X	X	X
WPAI-UC/WPAI-CD (n)	(P)									X			
PRO (IBDQ,EQ-5D) (n)	(P)									X			
12-lead ECG	(P)										X	X	
AE/SAE assessment (o)		X	X	X	X	X	X	X	X	X	X	X	X
Subject assessment of disease activity (p)		X	X	X		X		X		X	X		
Dosing (q)		X	X	X	X	X	X	X	X	X	X		
Clinical chemistry	(P)		X	X		X		X		X	X	X	X
Hematology	(P)		X	X		X		X		X	X	X	X
Coagulation	(P)										X	X	
Urinalysis	(P)										X	X	
Pregnancy test (r)	X (s)	X		X		X		X	X	X	X	X	X
FSH	(P)												
[redacted]													

Footnotes are on last table page.

Appendix A Schedule of Study Procedures: Q2W Dosing (continued)

STUDY PROCEDURES	Eligibility Assessment (b)	Treatment Weeks (+/- 1 week) (a)											
		Wk 0 (c) CLINIC	Wk 2 CLINIC	Wk 4 CLINIC	Wk 6 (d)	Wk 8 CLINIC	Wk 10, 12, 14 (d)	Wk 16 CLINIC (e)	Telephone Visits From Wk 16 (d)	Visits Every 8 Weeks From Wk 16 and Every 24 Weeks After Wk 72 CLINIC (e)	Unscheduled Visit (a,e,f)	Final Visit/ET (g) CLINIC	Final Safety Follow-up (h) CLINIC
[redacted]													
Stool sample (w)										X (t)	X (w)		

Note: Day = day after the last dose.
(P)=obtained from previous study, h=hours, Wk=week.
(a) Subjects (not including those in Japan) will switch to PFS+AI at any scheduled or unscheduled visit when they become available at the site. An additional visit for training of self-injection can be set as needed. For sites not able to conduct onsite visits due to a pandemic (eg, COVID-19 or other similar pandemic), alternative methods for conducting visits (eg, video conferencing, telephone visits) may be used with prior approval by the sponsor or designee. Safety laboratory assessments (ie, clinical chemistry and hematology) should be conducted at least every 24 weeks. If a clinic visit must be conducted via alternative methods due to a pandemic (eg, COVID-19), safety laboratory assessments may be done using local laboratories if it is feasible for the subject to visit a local laboratory sooner than the study site for sample collection. See Section 9.3.7 for guidance on alternative methods for conducting study procedures due to a pandemic.
(b) Subjects eligibility for OLE will be assessed at ET/Week 52 of the previous study (MLN0002SC-3027 or MLN0002SC-3031), or at the relevant visit for Week 14 responders. If the subject is deemed eligible they will undertake informed consent for MLN0002SC-3030. Week 0 dosing will occur in accordance with Section 6.1 of this protocol.
(c) The first 2 doses will be administered in the clinic. For Q2W subjects, clinic visits will be at Weeks 0, 2, 4, 8 and then every 8 weeks until at least Week 72 or the next visit that is a multiple of 24 (eg, Week 96, 120, 144, etc), and then every 24 weeks thereafter.
(d) Telephone visit: subjects will be contacted via telephone prior to dosing outside of the clinic every 2 weeks.
(e) *Japan only:* subjects can switch to PFS+NSD or PFS+AI at any scheduled or unscheduled visit beginning at the Week 16 visit. An additional visit for training of self-injection (eg, 2 weeks after the switch) can be set as needed.
(f) Subjects seen at an unscheduled visit for disease exacerbation or SAE will complete the Unscheduled Visit assessments.
(g) Final Visit/ET: The duration of vedolizumab SC treatment will vary by subject based on continued benefit, but will be until vedolizumab SC is available in the subject's country commercially or through other access programs.
(h) Final Safety Follow-up Visit: Subjects will return 18 weeks after the last dose of vedolizumab SC for final safety assessments.
(i) Including reassessment of female reproductive status.
(j) A physical examination will be done at Week 0 if Week 0 is not the same day as ET/Week 52 of the parent study. Physical examinations will then be performed at Weeks 2, 4, 8, 16 and every 8 weeks until at least Week 72 or the next visit that is a multiple of 24 (eg, Week 96, 120, 144, etc), and then every 24 weeks thereafter. Clinically significant findings will be recorded as an AE if it starts after the first dose of study drug on this study.
(k) Vital signs will also be measured on dosing days prior to dosing in the clinic. Height may be taken from the parent study.
(l) The PML checklist will be administered in person at dosing occurring in the clinic during scheduled visit. The PML subjective checklist will be administered over the phone when subject is injecting outside of the clinic. If the subject is escalating to QW dosing at an Unscheduled Visit for disease exacerbation, then the PML checklist will be administered prior to dosing.
(m) Monitoring of concomitant medications and concomitant procedures will begin at enrollment. Any medications that are ongoing at the end of the parent study and that are still present at the time of enrollment into the MLN0002SC-3030 study will be recorded in the eCRF for Study MLN0002SC-3030.

(n) WPAI-UC/WPAI-CD and PRO (IBDQ, EQ-5D): To be performed at Week 24 and every 24 weeks thereafter while on study.
(o) Collection of AEs will begin following the signing of the informed consent and will continue through to Final Safety Visit. Collection of all SAEs starts at enrollment and will continue through to Final Safety Visit.
(p) Disease activity is assessed by partial Mayo score for UC subjects and by HBI for CD subjects in this study and is recorded at the clinic visits.
(q) Dosing in this study (Week 0) will occur no more than 4 weeks after the last dose of study drug for completers/ET in Study MLN0002SC-3027 or MLN0002SC-3031. For Week 14 responders from the parent study, Week 0 will occur no more than 1 week (±7 days) from Week 14 in Study MLN0002SC-3027 or MLN0002SC-3031. From Week 16, continue Q2W dosing. Subjects will return to the clinic every 8 weeks to receive an 8-week supply of vedolizumab SC for administration at home.
(r) Pregnancy test: All females of child bearing potential must have a serum pregnancy test at the ET/Final Safety Visit. A urine pregnancy test will be completed for all females of child bearing potential prior to each dose of study drug injected during clinic visits and monthly prior to home dosing.
(s) For Week 14 responders from the parent study, a serum pregnancy test will be performed during the eligibility assessments.

[redacted]

(w) A stool sample for culture, ova and parasite evaluation, and *C difficile* assay will be obtained at any time point during the study when a subject becomes symptomatic, including worsening or return of disease activity (if indicated).

Appendix B Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities:

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

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

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

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

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

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

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

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

Adapted from: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987; 317 (26):1625-9.

Appendix F HBI for the Assessment of Crohn's Disease Activity

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

Appendix G Protocol History

Date	Amendment Number	Amendment Type	Region
20 October 2020	10	Substantial	Global
24 October 2018	09	Substantial	Belgium, Denmark, Germany, Hungary, Italy, Lithuania, Poland, Romania, Spain, Sweden, United Kingdom
16 October 2018	08	Nonsubstantial	Belgium, Denmark, Germany, Hungary, Italy, Lithuania, Poland, Romania, Spain, Sweden, United Kingdom
23 April 2018	07	Substantial	Global
28 March 2018	06	Substantial	Japan
08 November 2016	05	Substantial	Global
01 August 2016	04	Substantial	Global
12 May 2016	03	Substantial	Global
10 February 2016	02	Substantial	Global
04 September 2015	01	Substantial	Global
27 February 2015	Initial Protocol	Not applicable	Global

Rationale for Amendment 09

This amendment applies to Voluntary Harmonisation Process countries only (Belgium, Denmark, Germany, Hungary, Italy, Lithuania, Poland, Romania, Spain, Sweden, United Kingdom). The primary reason for this amendment was to include the option for subjects to switch to the PFS+AI presentation when they become available at the site. Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study were included for clarification and administrative purposes only.

Changes in Amendment 09

1. Included the option that subjects will switch to PFS+AI when this presentation becomes available at the site.
2. Updated the permitted medications to allow topical steroid treatment for new extraintestinal manifestations (only) of IBD after approval by the sponsor.

[redacted]

4. Updated the visit window for the QW dosing group in alignment with Amendment 07.

Rationale for Amendment 08

Amendment 07 was not approved in countries that follow the Voluntary Harmonisation Process (Belgium, Denmark, Germany, Hungary, Italy, Lithuania, Poland, Romania, Spain, Sweden, United Kingdom). Therefore, this amendment was developed to apply to those countries only. The

primary reason for this amendment was to specify an interim analysis and report will be generated to support regulatory filings and updates.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study were included for clarification and administrative purposes only.

Changes in Amendment 08

[redacted]

3. Included specification that interim analyses and reports will be generated to support regulatory filings and updates, in alignment with Amendment 07.

Rationale for Amendment 07

The primary reason for this amendment was to include the option for subjects to switch to the PFS+AI presentation when they become available at the site. Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study were included for clarification and administrative purposes only.

Changes in Amendment 07

1. Included the option that subjects can switch to vedolizumab IV if vedolizumab SC is not available.
2. Included the option that subjects will switch to PFS+AI when this presentation becomes available at the site.
3. Updated the permitted medications to allow topical steroid treatment for new extraintestinal manifestations (only) of IBD after approval by the sponsor.

[redacted]

6. Updated the visit window for the QW dosing group.
7. Included specification that interim analyses and reports will be generated to support regulatory filings and updates.

Rationale for Amendment 06

This amendment applied to Japan sites only. The primary reason for this amendment was to include the option for subjects at participating sites in Japan to switch to the commercial presentations when they become available at the site, and to study their ability to self-inject with these devices. Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study were included for clarification and administrative purposes only.

Changes in Amendment 06

1. Included the option that subjects at participating sites in Japan can switch to vedolizumab SC in the PFS+NSD or PFS+AI presentations available at the site when they become available. The ability of these subjects to self-inject with these devices will be studied.

Rationale for Amendment 05

The primary purpose of this amendment was to correct the amendment type for Amendment 04 to substantial. Minor grammatical and editorial changes were included for clarification purposes only.

Changes in Amendment 05

1. Amendment 04 was changed from nonsubstantial to substantial.
2. An administrative change was made to the sponsor address in Japan.
3. Typographical errors, punctuation, grammar, and formatting were corrected.

Rationale for Amendment 04

The primary purpose of this amendment was to update some inconsistencies in the Schedule of Study Procedures. The table was updated for clarity and consistency with the updates in the body of the protocol. Footnotes were also updated for clarity with the updates in the body of the protocol. Minor grammatical and editorial changes were included for clarification purposes only.

Rationale for Amendment 03

The primary purpose of this amendment was to update the protocol to include additional information for clarification. Other minor changes in procedures were proposed. Minor grammatical and editorial changes were included for clarification purposes only.

Changes in Amendment 03

1. Clarification of secondary endpoints.
2. Addition of inclusion criterion #4, where subjects who had participated in either parent study and, in the opinion of the investigator, tolerated the study drug well could participate in this study. Subjects who did not achieve a clinical response at Week 6 and were not randomized into the maintenance phase, but received a third open-label vedolizumab IV infusion and showed achieved a clinical response at Week 14, were eligible to participate in the study.
3. Clarification added to exclusion criteria.
4. Update and additional text added to Section 7.3.1 Permitted Medications and Treatments.
5. Clarification to Section 9.1.6.1 Diary Completion and Review to specify that all subjects entering from the parent studies must complete the diaries.

Rationale for Amendment 02

The primary purpose of this amendment was to update the protocol regarding inclusion of a benefit-risk assessment, to update to the expected treatment duration, and to clarify the colorectal cancer screening surveillance requirements.

Changes in Amendment 02

1. Benefit-risk assessment was included in new Section 4.3.
2. Expected treatment duration was updated to a maximum of 5 years.
3. Inclusion criterion #7 was updated to clarify colorectal cancer surveillance requirements.

Rationale for Amendment 01

The primary purpose of this amendment was to update the protocol regarding inclusion of a Product Complaints section; update the clinical pharmacology background and [redacted]; and make minor clarifications in the inclusion/exclusion criteria. Other minor changes in procedures were also proposed. Minor grammatical and editorial changes were included for clarification purposes only.

Changes in Amendment 01

1. Clinical pharmacology information.

   Justification: Updates in the clinical pharmacology background and [redacted] reflect the dosing simulation modeling.

2. Inclusion/exclusion criteria.

   Justification: Minor clarifications to assist with correct selection of participating subjects.

3. Product complaints.

   Justification: This section was added to clarify the process for reporting product complaints during the study.

4. Correction of inconsistencies within the original protocol.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	26-Oct-2020 15:53 UTC
[redacted]	Clinical Pharmacology Approval	27-Oct-2020 13:01 UTC
[redacted]	Clinical Science Approval	28-Oct-2020 22:44 UTC