Title: An Open-Label, Single-Center, Phase 1 Study to Determine the Pharmacokinetics of Single Intravenous Dose of Vedolizumab 300 mg in Healthy Adult Chinese Subjects

NCT Number: NCT03329209

Protocol Approve Date: 10 May 2018

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

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

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

PROTOCOL

An Open-Label, Single-Center, Phase 1 Study to Determine the Pharmacokinetics of Single Intravenous Dose of Vedolizumab 300 mg in Healthy Adult Chinese Subjects

Phase 1 Vedolizumab PK study in China

Sponsor:	Takeda Development Center Asia, Pte. Ltd. 21 Biopolis Road Nucleos North Tower, Level 4 Singapore 138567		
Study Number:	Vedolizumab-1014		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	Vedolizumab IV		
Date:	10 May 2018	**Amendment Number:**	02

Amendment History:

Date	Amendment Number	Region
08 July 2015	Initial version	Asia
01 June 2017	01	Asia
10 May 2018	02	Asia

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

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 should be provided to the site.

Contact Type / Role	China Contact
Serious adverse event and pregnancy reporting Medical Monitor (medical advice on protocol and compound) Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories, as applicable can be found on the signature page.

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

PPD

INVESTIGATOR AGREEMENT

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

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

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

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Provence)

_____

Location of Facility (Country)

1.3 Protocol Amendment 02 Summary of Changes

Rationale for Amendment 02

This document describes the changes in reference to the protocol incorporating Amendment No. 02.

The primary reason for this amendment is to provide clarification to some administrative terms of the protocol Vedolizumab-1014 amendment 01 (dated 01 Jun 2017).

For specific descriptions of text changes and where the changes are located, see Appendix F.

Changes in Amendment 02

1. Clarification for confirmation of entry criteria, including test results.
2. Clarification of the in-clinic diet.
3. Change in definition of timing for significant protocol deviation.
4. Revised Section 8.2 (Investigational Drug Assignment and Dispensing Procedures), to specify that the 3-digit Subject ID number will be used instead of 4-digit enrollment number.
5. Clarify list of serum chemistry laboratory tests.
6. Clarify timing of vital signs.
7. Clarification of dosing.
8. Deletion of collection and storage of specimens for genome/gene analysis.
9. Correction in approximate blood values to be drawn.
10. Clarification of timing for when subjects are assessed for signs and symptoms of PML.
11. Deletion of text regarding samples collected outside the window not being considered a protocol deviation.
12. Modifications to Appendix A (Schedule of Study Procedures) to add Day 8 timepoint for serum pregnancy test (hCG) and Final Visit/ET timepoint for dispensing PML Wallet Card.

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="3">Name of Sponsor(s):
Takeda Development Center Asia, Pte. Ltd.</td><td colspan="3">Compound:
Vedolizumab IV</td></tr>
<tr><td colspan="3">Title of Protocol: An Open-Label, Single-Center, Phase 1 Study to Determine the Pharmacokinetics of Single Intravenous Dose of Vedolizumab 300 mg in Healthy Adult Chinese Subjects</td><td colspan="2">IND No.:
Not Applicable</td><td>EudraCT No.:
Not Applicable</td></tr>
<tr><td colspan="3">Study Number: Vedolizumab-1014</td><td colspan="3">Phase: 1</td></tr>
<tr><td colspan="6">Study Design:
This is an open-label, single-center, phase 1 study to determine the pharmacokinetics (PK) of single intravenous dose of vedolizumab 300 mg in healthy adult Chinese subjects.
Subjects will be kept in the study unit for at least 3 days after the start of infusion on Day 1 for safety and PK assessments before discharge. The confinement period will be a minimum of 3 days to a maximum of 7 days.
Subjects will return to the study unit periodically according to the predetermined PK sampling scheduled until Day 127 or Early Termination (ET). Additionally, subjects will be required to participate in a long-term follow-up (LTFU) safety survey by telephone, 6 months after the dose of study drug.
The total duration on study for each subject will be approximately 7.0 months, including Screening.</td></tr>
<tr><td colspan="2">Screening</td><td>Treatment</td><td colspan="3">Follow-Up</td></tr>
<tr><td rowspan="2">Days
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(Check-in)</td><td>Day 1</td><td>Day 2-3</td><td>Days 10, 15, 29, 43, 64, 85, 106 (a)</td><td>Final Visit/ET Day 127 (b)</td><td>LTFU Safety Survey (c) Day 168</td></tr>
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<tr><td></td><td colspan="2">←——Confinement ——————→</td><td colspan="3"></td></tr>
<tr><td colspan="6">(a) Days 10 and 15 have a ±1-day window. Days 29 and 43 a ±2-day window, and Days 64, 85, 106 and 127/ET all have a ±3 day window.
(b) In case abnormal, clinically significant findings are observed upon discharge, subjects may be brought back to the clinic for re-evaluation per investigator's discretion.
(c) Subjects will be followed poststudy by telephone call at Day 168 (±3days) after the last dose of study drug to administer a LTFU safety survey.</td></tr>
<tr><td colspan="6">Primary Objective:
To assess the PK of vedolizumab following a single intravenous infusion in healthy adult Chinese subjects.
Secondary Objectives:
To evaluate the safety and tolerability of a single intravenous infusion of vedolizumab in healthy adult Chinese subjects.</td></tr>
<tr><td colspan="6">Subject Population: Healthy male and female adult Chinese subjects aged 18 to 45 years, inclusive, at the time of informed consent.</td></tr>
<tr><td colspan="3">Number of Subjects:
Estimated Total: 16 subjects dosed</td><td colspan="3">Number of Sites:
Estimated total: 1 site in China</td></tr>
<tr><td colspan="3">Dose Level(s):
Single dose of vedolizumab IV 300 mg</td><td colspan="3">Route of Administration:
IV infusion over approximately 30 minutes</td></tr>
<tr><td colspan="3">Duration of Treatment:
Single dose on Day 1</td><td colspan="3">Period of Evaluation:
196 days including Screening Period</td></tr>
</table>

Main Criteria for Inclusion:

Healthy male or non-pregnant, non-lactating female Chinese subjects aged 18-45 years inclusive, who are willing and able to comply with the study schedule and assessments. The subject weighs at least 50 kg and has a body mass index (BMI) of between 19.0 and 26.0 kg/m^2, inclusive at Screening.

Main Criteria for Exclusion:

The subject has received any investigational compound within 30 days prior to dosing of study medication or history of treatment with another monoclonal antibody within 6 months to dosing of study medication.

The subject has received vedolizumab in a previous clinical study or as a therapeutic agent.

The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine disease, or psychiatric disease, or other abnormality, which may impact the ability of the subject to participate or potentially confound the study results.

The subject has a known hypersensitivity to any component of the formulation of vedolizumab IV.

The subject is unable to attend all study days or comply with protocol requirements.

In addition, subject may not use any excluded medication or supplement to be outlined in the protocol.

Main Criteria for Evaluation and Analyses:

The primary endpoints for this study are:

- Maximum observed serum concentration (C_{max}).
- Area under the serum concentration-time curve from time 0 to time of the last measureable concentration (AUC_{last}).
- Area under the serum concentration-time curve from time 0 to infinity (AUC_{∞}).

The secondary endpoints for this study are:

- Proportion of subjects with positive anti-vedolizumab antibody (AVA) during the study.
- Proportion of subjects with positive neutralizing AVA during the study.
- Safety assessment: Percentage of subjects with adverse events (AEs), percentage of subjects with adverse events of special interest (AESIs, including serious infections, including opportunistic infection such as progressive multifocal leukoencephalopathy (PML), liver injury, malignancies and infusion related reactions and hypersensitivity), percentage of subjects with serious adverse events (SAEs), number of subjects with markedly abnormal vital signs, number of subjects with markedly abnormal laboratory tests (clinical chemistry, hematology, coagulation, urinalysis), and number of subjects with markedly abnormal 12-lead electrocardiograms (ECGs).

Statistical Considerations:

Descriptive statistics will be used to summarize serum concentrations of vedolizumab over each scheduled sampling time. Individual serum concentration-time data will be presented as listings.

Descriptive statistics will be used to summarize serum PK parameters of vedolizumab. Individual serum PK parameters will be presented in a data listing.

All AEs will be presented in listings: AEs and AESIs will be summarized. Individual results of laboratory tests (hematology, chemistry, and urinalysis), vital signs, and ECGs will be listed, and observed values will be summarized for every collection time point. Physical examination findings will be presented in the data listings.

The proportion of subjects with positive AVA will be summarized by the scheduled sampling time. The proportion of subjects with neutralizing AVA by the end of the study will be summarized. Titers of AVA and neutralizing AVA will be listed.

Additional analyses may be performed as needed.

Sample Size Justification: A sample size of 16 subjects in this study is deemed sufficient to determine the PK and safety profile of a single dose of vedolizumab IV in healthy adult Chinese subjects. This sample size is not based on statistical considerations

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.

3.2 Principal Investigator

PPD

3.3 List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{∞}	area under the serum concentration-time curve from time 0 to infinity
AUC_{last}	area under the serum concentration-time curve from time 0 to time of the last measureable concentration
AVA	anti-vedolizumab antibody
BMI	body mass index
bpm	beats per minute
CD	Crohn's disease
C_{max}	maximum observed serum concentration
CRO	contract research organization
CS	clinically significant
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
ET	Early Termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IAC	Independent Adjudication Committee
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
JCV	John Cunningham virus
LFT	liver function test
LTFU	long-term follow up
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities

NCS	Not Clinically Significant
PGx	pharmacogenomics
PI	principal investigator
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PTE	pretreatment event
Q8W	once every 8 weeks
QTcB	QT interval with Bazett correction method
QTcF	QT interval with Fridericia correction method
RAMP	Risk Assessment and Minimization Program for PML
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
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
VCAM-1	vascular cell adhesion molecule
WHODRUG	World Health Organization Drug Dictionary

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

Vedolizumab (also referred to as MLN0002 or Entyvio) is a humanized immunoglobulin G1 monoclonal antibody directed against the human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$integrin mediates lymphocyte trafficking to the gastrointestinal (GI) mucosa and gut-associated lymphoid tissue through adhesive interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa [1-4]. Vedolizumab binds the $\alpha_4\beta_7$ integrin, antagonizing its adherence to MAdCAM-1 and as such, impairs the migration of gut homing leukocytes into GI mucosa. Due to its gut selective immunomodulatory properties [5], vedolizumab has been developed as a treatment for ulcerative colitis (UC) and Crohn's disease (CD).

The effectiveness and safety of vedolizumab intended for intravenous (IV) use (vedolizumab IV, vedolizumab for injection, for intravenous use) for UC and CD have been established in pivotal clinical trials in subjects who had not responded adequately to corticosteroids, immunomodulators, or tumor necrosis factor-alpha (TNF-α) antagonists [6-8].

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

Single- and multiple-dose pharmacokinetics (PK) of vedolizumab have been studied in healthy subjects and in patients with moderately to severely active UC or CD. Similar PK was observed in healthy subjects, UC patients, and CD patients. Vedolizumab exhibits target-mediated drug disposition; hence, its elimination is characterized by linear and nonlinear processes. Following IV infusion, the serum concentrations of vedolizumab 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. Vedolizumab was not detected in the cerebrospinal fluid at 5 weeks after a single IV administration in healthy subjects.

Different intrinsic and extrinsic factors, including age, body weight, serum albumin, severity of disease state, prior treatment with TNF-α antagonist, coadministration with immunomodulators (including azathioprine, 6-mercaptopurine, methotrexate) or aminosalicylates, did not impact the PK of vedolizumab in subjects with UC or CD based on population PK analysis, as such, no dose adjustment is recommended for any of the above-mentioned covariates. PK of vedolizumab was similar between Japanese and Western subjects.

As of July 2014, vedolizumab IV has been granted marketing approval in the United States and additional countries for the treatment of adult patients with moderately to severely active UC or

CD, who have failed conventional treatment, including immunomodulators, corticosteroids, or TNF-α antagonists. The recommended dosage for UC and CD is 300 mg vedolizumab IV infused over approximately 30 minutes at Weeks 0, 2, and 6, then once every 8 weeks (Q8W) thereafter.

4.2 Rationale for the Proposed Study

This phase 1 study is designed to meet the requirements of the China Food and Drug Administration (CFDA) for registration of vedolizumab IV in China. The effectiveness and safety of vedolizumab for UC and CD have been established in global clinical trials in support of marketing approval in the United States and additional countries. The main objective of this open-label, single-dose study is to assess the PK of vedolizumab in Chinese subjects and to allow comparison with the clinical data previously acquired in other regions, including North America, Europe, and Japan, etc. The results from this phase 1 study and the proposed phase 3 efficacy and safety studies in Chinese subjects with moderately to severely active UC or CD, along with available clinical data in other regions, will be used to support the registration of vedolizumab IV in China.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To assess the PK of vedolizumab following a single IV infusion in healthy adult Chinese subjects.

5.1.2 Secondary Objective

- To evaluate the safety and tolerability of a single IV infusion of vedolizumab in healthy adult Chinese subjects.

5.2 Endpoints

5.2.1 Primary Endpoints

- Maximum observed serum concentration (C_{max}).
- Area under the serum concentration-time curve from time 0 to time of the last measureable concentration (AUC_{last}).
- Area under the serum concentration-time curve from time 0 to infinity (AUC_{∞}).

5.2.2 Secondary Endpoints

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

5.2.3 Safety Endpoints

- Safety assessment: Percentage of subjects with adverse events (AEs), percentage of subjects with adverse events of special interest (AESIs, including serious infections, including opportunistic infection such as progressive multifocal leukoencephalopathy (PML), liver injury, malignancies and infusion related reactions and hypersensitivity), percentage of subjects with serious adverse events (SAEs), number of subjects with markedly abnormal vital signs, number of subjects with markedly abnormal laboratory tests (clinical chemistry, hematology, coagulation, urinalysis), and number of subjects with markedly abnormal 12-lead electrocardiograms (ECGs).

5.2.4 Additional Endpoints

- Time of first occurrence of C_{max} (t_{max}).
- Terminal disposition phase half-life ($t_{1/2z}$).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is an open-label, single-center, phase 1 study to determine the PK of single dose of vedolizumab IV 300 mg in healthy adult Chinese subjects. The number of subjects to be dosed in the study is 16. Since vedolizumab is intended to be used by both male and female subjects with UC or CD, effort will be made to enroll an equal number of male and female subjects in this study.

Subjects will be kept in the study unit for at least 3 days after the start of infusion on Day 1 for safety and PK assessments before discharge. The confinement period will be a minimum of 3 days and a maximum of 7 days.

Subjects will return to the study units periodically according to the predetermined PK sampling scheduled until Day 127 or Early Termination (ET). Additionally, subjects will be required to participate in a long-term follow-up (LTFU) safety survey by telephone, 6 months after the dose of study drug. The total duration on study for each subject will be approximately 7.0 months, including screening.

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

<table>
<tr><th colspan="2">Screening</th><th>Treatment</th><th colspan="4">Follow-Up</th></tr>
<tr><td rowspan="2">Days
-28 to -2</td><td rowspan="2">Day -1
(Check-in)</td><td>Day 1</td><td>Day 2-3</td><td>Days 10, 15, 29, 43, 64, 85, 106 (a)</td><td>Final Visit/ET Day 127 (b)</td><td>LTFU Safety Survey (c) Day 168</td></tr>
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</table>

(a) Days 10 and 15 have a ±1 day window. Days 29 and 43 a ±2 day window, and Days 64, 85, 106 and 127/ET all have a ±3 day window.
(b) In case abnormal, clinically significant findings are observed upon discharge, subjects may be brought back to the clinic for re-evaluation per investigator's discretion.
(c) Subjects will be followed poststudy by telephone call at Day 168 (±3 days) after the last dose of study drug to administer a LTFU safety survey.

6.2 Justification for Study Design, Dose, and Endpoints

This is a single-center, open-label, single-dose study using vedolizumab IV 300 mg infused IV over 30 minutes. The objective of the study is to evaluate the PK of vedolizumab following a single IV infusion of 300 mg vedolizumab IV in healthy adult Chinese subjects. Vedolizumab IV 300 mg dosing at Weeks 0, 2, and 6, and Q8W thereafter is the recommended regimen for subjects with moderately to severely active UC or CD in the United States, European Union, and Australia, as well as the dose regimen being used in the ongoing phase 3 studies in UC and CD subjects in Japan and the planned dose regimen in the phase 3 studies in China.

Given the long half-life of vedolizumab (approximately 25 days), blood samples will be collected up to 18 weeks (>5 half-lives) to sufficiently assess vedolizumab PK after IV infusion. Since vedolizumab is intended to be administered Q8W during the maintenance phase in the phase 3 studies in China, the accumulation after repeated dosing is expected to be minimal. This is supported by the fact that the trough serum concentration of vedolizumab was maintained at similar levels after reaching steady state in the completed phase 3 studies. Based on the population PK analyses conducted for the completed clinical studies, vedolizumab PK is similar in healthy subjects, as well as in subjects with UC or CD. Therefore, a single-dose PK study in healthy subjects is considered sufficient to provide the estimates of the steady-state exposure of vedolizumab following multiple Q8W maintenance doses in UC or CD patients, and a multiple-dose design is not necessary.

The impact of race (Westerns vs Japanese) was assessed through cross-study comparison using noncompartmental PK parameters. The dose- and weight-normalized PK parameters observed in Japanese subjects with UC (Study CPH-001) were similar to those observed in Western subjects with UC (Study C13002), suggesting that there is no effect of race on the PK of vedolizumab. The preliminary results from a recently completed single dose bioavailability study in healthy Japanese and non-Japanese subjects (MLN0002SC-101) further confirmed the lack of race effect on vedolizumab PK.

The sample size of 16 subjects is considered sufficient to evaluate the PK profiles after single dose of vedolizumab IV in adult healthy Chinese subjects. This sample size is not based on statistical considerations.

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 compound, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of 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 dosing of study drug on Day 1.

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 including requesting that a subject fast for any laboratory evaluations.
3. The subject is a healthy male or nonpregnant, nonlactating female adult Chinese subject aged 18 to 45 years, inclusive, at the time of informed consent.
4. The subject weighs at least 50 kg and has a body mass index (BMI) from 19.0 to 26.0 kg/m^2, inclusive at Screening.
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 18weeks 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 and throughout the duration of the study and for a minimum of 18 weeks after last dose.

*Definitions and acceptable methods of contraception are defined in Section 9.1.9 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.10 Pregnancy.

7.2 Exclusion Criteria

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

1. The subject has received any investigational compound within 30 days prior to dosing of study medication or history of treatment with another monoclonal antibody within 6 months to dosing of study medication.
2. The subject has received vedolizumab in a previous clinical study or as a therapeutic agent.
3. 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 the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, GI, urologic, immunologic, endocrine disease, or psychiatric disease,

or other abnormality, which may impact the ability of the subject to participate or potentially confound the study results.

5. The subject has a known hypersensitivity to any component of the formulation of vedolizumab IV.
6. The subject has one or more positive response on the PML subjective symptoms checklist at Screening or before dosing on Day 1.
7. The subject has a positive result for drugs or alcohol abuse at Screening or Check-in (Day -1).
8. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the Screening visit or is unwilling to agree to abstain from alcohol for 48 hours prior to Check-in (Day -1) throughout the confinement and for 48 hours prior to each clinic visit and drugs throughout the study.
9. The subject has taken any excluded medication listed in Section 7.3.
10. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 18 weeks after the last dose in the study; or intending to donate ova during such time period.
11. If male, the subject intends to donate sperm during the course of this study or for 18 weeks after the last dose of study medication.
12. The subject has evidence of current cardiovascular, central nervous system, hepatic, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma, hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking vedolizumab, or a similar drug in the same class, or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, seizure disorders, and cardiac arrhythmias.
13. The subject has had a surgical procedure requiring general anesthesia within 30 days before the initial Screening Visit or is planning to undergo a surgery that requires general anesthesia during the study period (through Final Visit/Day 127).
14. The subject has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Day 1.
15. The subject has a positive test result for chronic hepatitis B virus*, hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody at Screening.
    * Subjects who are positive for hepatitis B surface antigen (HBsAg) will be excluded.
    For subjects who are negative for HBsAg but are positive for either surface antibodies and/or core antibodies, hepatitis B virus DNA polymerase chain reaction will be performed and any result that meets or exceeds detection sensitivity will be excluded.

16. The subject has active or latent tuberculosis (TB) as evidence by the following:
    i. A positive diagnostic TB test within 30 days of Day 1 defined as:
        1. A positive QuantiFERON test, or
        2. Two successive indeterminate QuantiFERON tests, or
        3. Chest X-ray within 3 months of Day 1 that is suspicious for pulmonary TB. Note: subjects with documented previously treated TB, which was successful, with a negative QuantiFERON test, can be included in the study.
17. The subject has poor peripheral venous access.
18. The subject has donated or lost 450 mL or more of his or her blood volume (including serumpheresis), or had a transfusion of any blood product within 45 days prior to Day 1.
19. The subject has a Screening or Check-in (Day -1) abnormal clinically significant ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature by the principal investigator (PI).
20. The subject has a supine blood pressure outside the range of 90 to 140 mm Hg for systolic and 50 to 90 mm Hg for diastolic, confirmed with 1 repeat testing within a maximum of 5 minutes, at the Screening Visit or Check-in (Day -1).
21. The subject has a resting heart rate outside of the range of 45 to 90 beats per minutes (bpm), confirmed with 1 repeat testing within a maximum of 5 minutes, at the Screening Visit or Check-in (Day-1).
22. The subject has a QT interval with Fridericia correction method (QTcF)>430 ms (males) or >450 ms (females) or PR outside the range 120 to 220 ms, confirmed with 1 repeat testing within a maximum of 5 minutes, at the Screening Visit or Check-in (Day -1).
23. The subject has abnormal Screening or Check-in (Day -1) laboratory values that suggest a clinically significant underlying disease or subject with the following lab abnormalities: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5 the upper limit of normal (ULN).
24. The subject is unable to attend all study days or comply with protocol requirements.

7.3 Excluded Medications, Dietary Products

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until completion of Final Visit (Day 127).

Table 7.a Prohibited Medications

28 days prior to Check-in (Day -1)
Prescription medications
OTC medications and supplements (a)
All live vaccines

OTC=over-the-counter.
(a) Occasional use of acetaminophen (≤1 g/day) or other medication as approved by Takeda on a case-by-case basis is allowed except on Day 1. Stable doses of multivitamins will be allowed.

During participation in the study, subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

7.4 Diet, Fluid, Activity Control

In the clinic, subjects will be provided 3 standard meals. and 2 snacks per day, each meal containing approximately 30% fat (relative to the total calories). The menu of the standardized meals from the clinical research site needs to be approved by Takeda before the implementation. The meals served on the day of dosing should be similar in nutritional content for each subject in the study. The study menu should be recorded and submitted to the study file with a copy provided with a copy provided to the sponsor.

If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence followed by the study procedure and then the meal.

Subjects will be advised to refrain from strenuous exercise from 72 hours before Check-in and throughout the confinement period of the study.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

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

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.

    - Liver Function Test (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 9.1.8), 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 dosing 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. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the 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).
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 9.1.10.
7. Other.

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

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the ET Visit. Discontinued or withdrawn subjects will not be replaced but additional subjects may be enrolled as needed.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Vedolizumab For Injection, For Intravenous Use

The study sites will be supplied by the sponsor with the following medication in an open-label manner: vedolizumab IV 300 mg/vial, for single use, in 20 mL vials. The study medication will be provided in a glass vial as a lyophilized solid formulation for reconstitution using sterile water. Each vial will be packaged in an appropriately labeled single vial carton.

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

8.1.2 Storage

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

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

8.1.3 Dose and Regimen

The investigator or investigator's designee will instruct the subject on dosing procedures.

All dosing will occur while subjects are in the clinic under the supervision of the PI or designees as indicated in Table 8.a.

Table 8.a Dose and Regimen

Treatment Group	No. of Subjects	Treatment
1	16 subjects dosed	300 mg vedolizumab IV, infusion over 30 min.

8.1.4 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 eCRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

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

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

8.2 Investigational Drug Assignment and Dispensing Procedures

The 3-digit subject number which is assigned at the time the informed consent is obtained, will be assigned by clinic site personnel in sequential order and which is used for all other procedures to identify the subjects throughout the study, as well as to facilitate the prelabeling of PK samples, contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

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

The 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 IV 300 mg), 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. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

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

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot number used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

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

The investigator or designee must record the current inventory of all sponsor-supplied drugs (vedolizumab IV 300 mg) 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, expiry and/or retest date, date and amount dispensed, including 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.

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.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

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, including requesting that a subject fast for laboratory evaluations.

A unique subject identification (ID) number (Subject ID = Site number + subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, race as described by the subject, alcohol use, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) GI system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as Not Clinically Significant (NCS) or Clinically Significant (CS) by the investigator and recorded in the source document and eCRF. All CS findings/changes will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF described in Section 10.0 or Section 9.1.7.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the investigational drug (Day 1) must be assessed as NCS or CS by the investigator and recorded in the source document and eCRF. Any

CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF described in Section 10.0.

9.1.4 Weight, Height and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below. The Takeda standard for collecting height is centimeters without decimal places and for weight it is kg with 1 decimal place. BMI should be derived as:

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

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then $BMI=79.2/1.76^2=25.5$ kg/m^2

9.1.5 Vital Sign Procedure

Vital signs (temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Check-in (Day -1), Day 1 (predose, and within ±5 minutes of 1 hour postdose and within ±30 minutes of 8 hours postdose), Days 2, 8, 10(±1), 15 (±1), 29 (±2), 43(±2), 64 (±3), 85 (±3), 106 (±3), and Final Visit Day 127(±3)/ET. For Days 1 and 2, heart rate and blood pressure will be measured after 5 minutes supine and again at 1 and 3 minutes after standing. For Days 8, 10(±1), 15 (±1), 29 (±2), 43(±2), 64 (±3), 85 (±3), 106 (±3) and Final Visit Day 127(±3)/ET, heart rate and blood pressure will be measured after 5 minutes supine only.

9.1.6 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. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

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

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be taken following a minimum 10-hour overnight fast on the days stipulated in the Schedule of Study Procedures (Appendix A).

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

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Special
RBCWBC with differential [% and absolute] Hemoglobin Hematocrit Platelets PT/INR (b)	ALT Albumin Alkaline phosphatase AST Total bilirubin Direct bilirubin Total protein Creatinine Blood urea Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate or Carbon dioxide Calcium	pH Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis (only if positive dipstick results): RBC/high power field WBC/high power field Epithelial cells, casts etc	QuantiFERON test for TB (a)
Serum		**Drug and Alcohol Screen**	
Serum hCG (c) AVA **At Screening Only:** Hepatitis panel, including HBsAg, HBsAb, HBcAb, anti-HCV and HIV (d) FSH (e)		Drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine (f) Breathalyzer - Alcohol	

FSH=follicle-stimulating hormone, GGT=γ-glutamyl transferase, HBcAb=hepatitis B core antibody, hCG=human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cells, WBC=white blood cells.
(a) Performed at Screening only. All subjects must have documented evidence of a negative QuantiFERON test at Screening.
(b) Prothrombin time/INR to be performed at Screening and last Study Visit (Day 127).
(c) Serum hCG pregnancy test will be done on all female subjects of childbearing potential at Screening, Check-in (Day -1), Day 8 and at Final Visit Day 127/ET.
(d) If subject is negative for HBsAg but is positive for either surface antibodies and/or core antibodies, hepatitis B virus DNA polymerase chain reaction will be performed.
(e) FSH level will be obtained for female subjects at Screening if they are postmenopausal by history (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) and not surgically sterile. The FSH result must be >40 IU/L for the subject to be permitted not to use adequate contraception.
(f) Subjects who do not meet the requirement for cotinine test can still be considered for recruitment at the discretion of the investigator.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted.

(Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study 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).

9.1.9 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 (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 are:

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, regular serum hCG pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm/ova donation as part of the study procedure (Appendix A). In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative serum hCG pregnancy test at Check-in (Day -1).

In addition, male subjects must be advised not to donate sperm from signing of informed consent to 18 weeks after the last dose of study medication.

9.1.10 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug (vedolizumab IV) should be immediately discontinued. 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, eg, after Day 1or 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 and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies 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.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded at Screening Visit, Check-in (Day -1), Day 1 (predose [within 0.5 hours prior to dosing] and at 8 hours after the start of infusion, Day 8 and Final Visit Day 127 (±3)/ET. When ECG recording is scheduled for the same visit day as blood draws (eg, PK or AVA sampling), the ECG recording should be collected before the blood sample. Single ECGs will be taken for all applicable visits. Additional unscheduled ECGs may be recorded where clinically necessary for subject safety.

ECGs will be read automatically and also, the investigator or sub-investigator will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. All 12-lead ECGs will be stored for manual measurement of intervals, if necessary. Twelve-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS interval, QT interval, QTcF and QT interval with Bazett correction method (QTcB) intervals. Paper ECG traces will be recorded for 10 seconds at a standard paper speed of 25 mm/sec and gain of 10 m/mV or digital recordings will be used.

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. If the original ECG is printed on thermal paper, the ECG report must be photocopied and certified. The photocopy will be filed with the original ECG in source.

9.1.12 Immunogenicity Sample Collection

Blood specimens for determination of AVA will be collected at day 1 predose (within 0.5 hours prior to dosing), Days 10 (±1), 29 (±2), 43 (±2), 64 (±3), 85 (±3), 106 (±3) and 127(±3)/ET postdose. A sample will be assessed for neutralizing AVA if AVA is detected.

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

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

A blood sample for AVA assessment will also be obtained at the unscheduled visit for subjects experience an SAE.

9.1.13 Pharmacokinetic Sample Collection

9.1.13.1 Collection of Serum for Pharmacokinetic Sampling

Blood samples (one 5-mL sample per scheduled time) for PK analysis of vedolizumab will be collected into red-top Vacutainers for serum according to the schedule in Appendix A. Instructions for sample processing and shipment are provided in Appendix E.

Note: On Day 1, PK samples should not be collected from the arm where the vedolizumab IV infusion is performed. All PK samples should be collected as specified in Table 9.b even if the vedolizumab IV infusion is discontinued before the complete dose is administered to the subject.

Serial blood samples for determination of vedolizumab will be collected according to Table 9.b.

Table 9.b Collection of Blood Samples for Pharmacokinetic Analysis

Sample Type	Dosing Day	Time of Blood Sample Collection
Serum	1	Within 0.5 hour prior to the start of the IV infusion, 0.25 hour (15 minutes), 0.58 hour (35 minutes; 5 min after the end of infusion) and, 2, 8, 24, 72, 120, and 168 hours after the start of the infusion, and on Days 10 (±1), 15 (±1), 29 (±2), 43 (±2), 64 (±3), 85 (±3), 106 (±3), and Final Visit Day 127(±3)/ET.

The actual time of dosing administration and sample collection will be recorded on the source document and eCRF.

9.1.13.2 Bioanalytical Methods

Serum concentrations of vedolizumab will be measured using a validated assay.

9.1.14 Pharmacokinetic Parameters

The PK parameters of vedolizumab will be determined from the concentration-time profiles for all evaluable subjects using a non-compartmental analysis method. The PK parameters, including t_{max}, C_{max}, AUC_{last}, AUC_{∞}, and $t_{1/2z}$, will be determined from serum concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

Symbol/Term	Definition
AUC_{last}	Area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_{∞}	Area under the serum concentration-time curve from time 0 to infinity, calculated as $AUC_{\infty}=AUC_{last}+C_{last}/\lambda z$
C_{max}	Maximum observed serum concentration.
$t_{1/2z}$	Terminal disposition phase half-life, calculated as $\ln(2)/\lambda z$.
t_{max}	Time of first occurrence of C_{max}.

Additional PK parameters may be calculated as appropriate.

9.1.15 Tuberculosis Screening

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

9.1.16 PML Checklist

Staff will administer the subject PML checklist during Screening to exclude subjects with positive responses from enrolling into the study. The PML subjective checklist will be administered at Screening Visit, on Day 1 prior to dose, Day 127(±3)/ET Visit, and at any unscheduled visits.

Any subjects reporting signs or symptoms of PML will undergo objective testing and may be referred to a neurologist for a full evaluation, as described in the Risk Assessment and Minimization Program for PML (RAMP). The symptoms from a positive PML checklist will be recorded as an AE. Additional information and tools for the RAMP can be found in the Study Manual.

9.1.17 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF screen failure form.

The primary reason for screen 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
- Study termination.
- Other

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

If a subject fails screening, but is later successfully rescreened, the data for the subject will be entered as if these were 2 separate subjects. Therefore the data should be entered as follows:

1. The screen failure data should be entered as a screen failure subject.
2. Rescreened subjects should be assigned a new subject number and treated as a stand-alone subject.

9.1.18 Documentation of Study Entrance

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

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

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

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

9.3.1 Screening

Subjects will be screened within 28 days prior to the dosing of study medication. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.15 for procedures for documenting screening failures.

9.3.2 Study Entrance

Study entrance into the treatment phase will take place on Day 1.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for study entrance, the subject should be assigned to treatment as described in Section 8.2. Subjects will be administered a dose of study medication in the unit under the supervision of the investigator or designee, as described in Section 8.2. The procedure for documenting Screening failures is provided in Section 9.1.15.

9.3.3 Final Visit

The Final Visit will be performed on Day 127 (±3 days).

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

9.3.4 Early Termination

The reason for discontinuation must be documented in the source document and eCRF.

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

9.3.5 Follow-up

Additionally, upon completion of or early termination from the study, all subjects will participate in a LTFU safety questionnaire on Day 168 (±3 days). The questionnaire will be administered by telephone at 6 months from the last dose of study drug.

9.4 Biological Sample Retention and Destruction

The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The samples will be sent to a central laboratory that processes the blood sample 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.

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.

9.5 Blood Volume

Total blood sampling volume for an individual subject is shown in Table 9.c.

Table 9.c Approximate Blood Volume

Approximate Blood Volume					
	Sample Volume (mL)	Number of Samples			Total Volume (mL)
Sample Type		Screening	Day -1	Days 1 -127	
Safety Laboratory Samples	20	1	1	4	120
QuantiFERON	3	1	--	--	3
PK Samples	5	--	--	17	85
Immunogenicity Samples	8.5	--	--	8	68
Total Blood Sampling Volume					276

Subject may be asked to provide additional safety laboratory blood samples at the follow-up visit, as appropriate. If a catheter will be used for PK blood collection, 1 mL of extra blood may be discarded for each PK sample.

The maximum volume of blood at any single day is approximately 38.5 mL, and the approximate total volume of blood for the study is 276 mL.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

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

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study 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.

Overdose:

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

10.1.4 SAEs

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

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

Table 10.a Takeda Medically Significant AE List

Term	
Acute 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
	Neuroleptic malignant syndrome/malignant hyperthermia
	Spontaneous abortion/stillbirth and fetal death

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

10.1.5 Special Interest AEs

A Special Interest Adverse Event (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 10.2.1.3 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.

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.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Day 1) or until screen 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 (Day 1). Routine collection of AEs will continue until the Final Visit (Day 127±3).

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. 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 and time.
3. Frequency.
4. Severity.
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study medication (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.1.3 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 an special interest AE eCRF or an SAE Form. The Form should be completed and reported to the SAE reporting contact in Section 1.0 within 24 hours.

Hypersensitivity Reactions (Including Infusion-Related 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. Vedolizumab IV should be administered by 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 for 2 hours following the infusion at a minimum.

If signs or symptoms of an infusion-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) at the discretion of the investigator. Subjects with a severe or serious

administration-related reaction (eg, shortness of breath, wheezing, stridor, angioedema, life change in vital signs) must be withdrawn from the study (see Study Manual).

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

Serious Infection

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

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.

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

10.2.2 Collection and Reporting of SAEs

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

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

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

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

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

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

10.2.3 Reporting of Abnormal Liver 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 9.1.8 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 is 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, 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

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

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 Program for PML (RAMP Program)

Natalizumab (TYSABRI), another integrin receptor antagonist, has been associated with PML, a rare and often fatal opportunistic infection of the central nervous system. PML is caused by the John Cunningham virus (JCV) and typically only occurs in patients who are immunocompromised [9,10]. Natalizumab is a pan-α_4 integrin antagonist that binds to both the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins and inhibits cellular adhesion to vascular cell adhesion molecule-1 (VCAM-1) and MAdCAM-1 [11,12]. In contrast, vedolizumab binds to the $\alpha_4\beta_7$ integrin only [5] and inhibits adhesion to MAdCAM-1, but not VCAM-1. Although no cases of PML have been reported in clinical trials with vedolizumab to date, a risk of PML cannot be ruled out.

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

The RAMP is focused on early clinical detection and management of that specific safety risk, including the discontinuation of study drug, if applicable. Subjects are assessed for signs and symptoms of PML prior to the administration of 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 next dose of study drug will be held 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 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 RECORDKEEPING

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 CRFs (Electronic)

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 eCRF. 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 to eCRFs 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. Reasons for significant corrections should additionally be included.

The PI 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

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 Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last

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

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

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

13.1.1 Analysis Sets

Safety Set:

The safety analysis set will consist of all subjects who are enrolled and received 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

Pharmacokinetic Set:

The PK set will consist of all subjects who receive study drug and have at least 1 measurable serum concentration.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized. Summary statistics (number of subjects, mean, SD, median, minimum and maximum) will be generated for continuous variables (eg, age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (eg, gender, ethnicity, and race).

Demographic variables of screen failure subjects and reasons for screen failures will be summarized for subjects who are screened, but not enrolled in the study. Individual demographic characteristics, date of informed consent, and reason for screen failure will be listed.

13.1.3 Pharmacokinetic Analysis

Descriptive statistics will be used to summarize serum concentrations of vedolizumab over each scheduled sampling time. Individual serum concentration-time data will be presented as listings.

Descriptive statistics will be used to summarize serum PK parameters of vedolizumab. Individual serum PK parameters will be presented in a data listing.

More detailed description will be provided in the SAP.

13.1.4 Immunogenicity Analysis

The proportion of subjects with positive AVA will be summarized by the scheduled sampling time. The proportion of subjects with neutralizing AVAs by the end of the study will be

summarized. Titers of AVA and neutralizing AVA will be listed. The impact of AVA on PK and safety may be explored.

More detailed description will be provided in the SAP.

Additional analyses may be performed as needed.

13.1.5 Safety Analysis

The number and percentage of subjects with treatment-emergent adverse events (TEAEs) defined as any AEs, regardless of relationship to study drug), AESIs for vedolizumab (ie, serious infections including opportunistic infection such as PML, liver injury, malignancies, infusion-related or systemic reactions and hypersensitivity and SAEs, which occur on or after dosing in patients, will be summarized by MedDRA system organ class, 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. Data listings will be provided for all AEs (including PTEs for enrolled subjects), AEs leading to study drug discontinuation, AEs leading to study visit discontinuation, SAEs, and AEs resulting in death.

Baseline, postbaseline and change from baseline in clinical laboratory tests, vital signs and ECG results will be summarized. Subjects with markedly abnormal values for laboratory tests, vital signs and ECG results will be tabulated. The mapping of the subjects who meet the markedly abnormal value criteria will be listed as a table. Individual results for clinical laboratory tests, vital signs and ECG measures will be listed.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

A sample size of 16 subjects in this study is deemed sufficient to determine the PK and safety profile of a single dose of vedolizumab IV in healthy adult Chinese subjects. This sample size is not based on statistical considerations.

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 (CRO) 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 EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. Significant protocol deviations will be entered into the eCRF, which is reviewed by the study sponsor or designee.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Table 14.a defines the windows allowed for sample collections.

The Significant Protocol Deviation eCRF is to be completed for deviations that are identified the sponsor prior to the study. Protocol Deviation Forms are to be completed for PK samples collected outside of the following intervals:

Table 14.a Windows for PK Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 30 minutes predose	0 hour
±5	immediately postdose to ≤6 hours
±10	>6 hours to ≤12 hours postdose
±15	>12 hours to ≤24 hours
±30	>24 hours

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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 screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will {ship drug/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 Screening may occur.

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The 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 ID number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique ID number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent 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 screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor. Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

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Appendix A Schedule of Study Procedures

	Screening		Treatment	Follow up (a)												
Procedures or Observations	**Days -28 to -2**	**Check-in Day -1**	**Day 1**	**Day 2**	**Day 4**	**Day 6**	**Day 8**	**Day 10 (±1)**	**Day 15 (±1)**	**Day 29 (±2)**	**Day 43 (±2)**	**Day 64 (±3)**	**Day 85 (±3)**	**Day 106 (±3)**	**Final Visit Day 127 /ET/ (±3) (b)**	**LTFU Safety Survey Day 168/ (±3)**
Informed consent (c)	X															
Dispense PML wallet card	X														X	
Inclusion/exclusion criteria	X	X														
Demographics and medical history	X															
Medication history	X															
Chest X-ray	X															
QuantiFERON test (d)	X															
PML checklist (e)	X		X												X	
Follow-up safety questionnaire																X
Physical exam (f)	X	X	X				X			X					X	
Vital signs (g)	X	X	X	X			X	X	X	X	X	X	X	X	X	
Height, weight and BMI (h)	X	X												X		
Concomitant medications (i)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG (j)	X	X	X				X								X	
Laboratory evaluations (k)	X	X					X			X			X		X	

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Screening		Treatment	Follow up (a)											
Procedures or Observations	**Days -28 to -2**	**Check-in Day -1**	**Day 1**	**Day 2**	**Day 4**	**Day 6**	**Day 8**	**Day 10 (±1)**	**Day 15 (±1)**	**Day 29 (±2)**	**Day 43 (±2)**	**Day 64 (±3)**	**Day 85 (±3)**	**Day 106 (±3)**	**Final Visit Day 127 /ET/ (±3) (b)**	**LTFU Safety Survey Day 168/ (±3)**
Urine drug screen	X	X														
Alcohol screen (breathalyzer)	X	X														
PT/INR (l)	X														X	
Serum pregnancy test (hCG) (m)	X	X					X								X	
FSH (n)	X															
HBsAg, HBsAb, HBcAb, anti-HCV and HIV(1 & 2)	X															
Confinement (o)		X	X	X	X	X										
Study drug dosing			X													
AVA assessment (p)			X					**X**		X	X	X	X	X	X	
PK blood collection (q)			X	X	X	X	X	X	X	X	X	X	X	X	X	
PTE/AE assessment (r)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Footnotes are on the following page.

HBcAb=hepatitis B core antibody.
(a) Days 10 and 15 have a ±1 day window. Days 29 and 43 have a, ±2 day window. Days 64, 85, 106, 127/ET and 168 telephone call all have a ±3 day window.
(b) Procedures for subjects discontinued early. A PK sample should be collected at the ET Visit, if possible.
(c) Informed Consent must be signed before any study-specific procedures are performed.
(d) All subjects must have a negative QuantiFERON test at Screening. Initial indeterminate results should be repeated. A subject with 2 indeterminate results will be excluded.
(e) The PML checklist will be administered at Screening Visit, on Day 1 prior to dose, Day 127(±3)/ET Visit, and at any unscheduled visits.
(f) Physical examination performed at the Screening Visit, Check-in Day -1, Day 1, Day 8, Day 29 (±2) and at the Final Visit Day 127 (±3) or /ET. All physical examinations are to be performed by the PI or subinvestigator. CS findings on the physical examination that occur postdose of study drug will be recorded as AEs.
(g) Vital signs (temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Check-in (Day -1), Day 1 (predose, and within ±5 minutes at 1 hour postdose, and within ±30 minutes at 8 hours postdose), Days 2, 8, 15 (±1), 29 (±2), 43(±2), 64(±3), 85 (±3), Day 106 (±3), and Final Visit Day 127(±3)/ET. For Days 1 and 2, heart rate and blood pressure will be measured after 5 minutes supine and again at 1 and 3 minutes after standing. For Days 8, 15 (±1), 29 (±2), 43(±2), 64(±3), 85 (±3), Day 106 (±3) and Final Visit Day 127(±3)/ET, heart rate, and blood pressure will be measured after 5 minutes supine only.
(h) Height, weight and BMI will only be collected at Screening. Only weight will be collected at Check-in Day -1 and Day 106 (±3).
(i) Record all ongoing medications from Screening through Final Visit Day 127/ET.
(j) Standard 12-lead ECGs will be recorded at Screening Visit, Check-in (Day -1), Day 1 (predose [within 0.5 hours prior to dosing] and at 8 hours after the start of infusion, Day 8, and Final Visit Day 127 (±3)/ET. When ECG recording is scheduled for the same visit day as blood draws (eg, PK or AVA sampling), the ECG recording should be collected before the blood sample.
(k) Clinical laboratory tests (hematology, serum chemistry, and urinalysis) will require a minimum 10-hour overnight fast night prior to clinical laboratory tests with the exception of the Screening Visit.
(l) PT/ INR will be performed at the Screening Visit and Final Visit (Day 127/ET).
(m) For women of childbearing potential only. Includes pregnancy avoidance counseling.
(n) A FSH level will be obtained on postmenopausal women (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) and not surgically sterile. The FSH result must be 40>IU/L for the subject to be permitted not to use adequate contraception).
(o) The total confinement period will be a minimum of 3 days and a maximum of 7 days. Subjects should be considered clinically stable by the investigator or designee prior to discharge.
(p) Blood samples (one 8.5 mL sample per scheduled time) for determination of AVA will be collected at predose (within 0.5 hours prior to dosing), Days 10, 29 (±2), 43 (±2), 64 (±3), 85 (±3), 106 (±3) and 127(±3)/ET postdose. AVA positive samples will be further analyzed for neutralizing AVA. A blood sample for AVA assessment will also be obtained at the unscheduled visit for subjects experience an SAE.
(q) Blood samples (5 mL sample per scheduled time) for PK analyses of vedolizumab will be collected at predose (within 0.5 hour prior to the start of the IV infusion), 0.25 hour (15 minutes), 0.58 hour (35 minutes; 5 min after the end of infusion) and, 2, 8, 24, 72, 120, and 168 hours after the start of the infusion, and on Days 10 (±1), 15 (±1), 29 (±2), 43 (±2), 64 (±3), 85 (±3), 106 (±3), and Final Visit Day 127(±3)/ET.
(r) PTEs will be captured immediately following the signing of the informed consent at Screening until the start of the infusion. The routine collection of AEs will be captured from the start of infusion and will continue until the Final Visit (Day 127/ET). Any new AEs/SAEs (reported at Final Visit Day 127/ET) will be recorded in the eCRFs and site source document. Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

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 investigator agrees to assume the following responsibilities:

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

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

Appendix C Elements of the Subject Informed Consent

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

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 Screening and throughout the duration of the study, and for <X> weeks after last dose of study medication. 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 Screening and 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 Collection, Storage, and Shipment of Bioanalytical Samples

Instructions for Processing of Serum Samples for PK Vedolizumab Analysis

1. Collect 5 mL of venous blood into a Becton-Dickinson Vacutainer or equivalent manufacturer. For all Vedolizumab samples, blood samples should be collected into red-stopper Vacutainers which contain no anticoagulant. Direct venipuncture is the preferred method of blood collection.
2. Allow the red top Vacutainer to sit at room temperature for approximately 30 to 60 minutes (refer to product information for correct time) to ensure proper clot formation.
3. To separate the serum samples, centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 relative centrifugal force (RCF) in a room temperature centrifuge. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. To ensure a more homogeneous sample, all serum should first be transferred into 1 aliquot. From there, split the serum evenly between the 2 aliquots into polypropylene tubes. A minimum of 1.0 mL needs to be obtained for each sample. Labeling may include protocol number (Vedolizumab-1014), matrix (ie, serum), PK assay, analyte (Vedolizumab), randomization number, nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the serum samples immediately at approximately -70°C or lower. No more than 1 hour and 45 minutes must be allowed to elapse between collecting blood and freezing the serum sample.
6. Keep samples frozen at approximately -70°C or lower until shipment to the selected laboratory in China. "SET 1" samples will be shipped first on dry ice, followed by shipment of duplicate "SET 2" samples after "SET 1" samples have been received by the analytical laboratory.

Instructions for Processing of Serum Vedolizumab Samples Immunogenicity Testing

1. Collect 8.5 mL of venous blood into a Becton-Dickinson Vacutainer (Serum Separator Tube, red/gray top SST, catalog# 367988 or equivalent). Direct venipuncture is the preferred method of blood collection.
2. Invert sample 5 times immediately after the blood collection and allow the Vacutainer to sit at room temperature for approximately 30 minutes to ensure proper clot formation.
3. Centrifuge the sample at 1000 to 1300 x g for 10 to 15 minutes at room temperature to isolate serum.
   a) For swing bucket rotors centrifuge samples for 10 minutes.
   b) For fixed-angle rotors centrifuge samples for 15 minutes.
   c) Refer to the centrifuge manual for proper operation of the centrifuge.

d) If using blood collection tubes other than BD Vacutainer Serum Separator Tube, follow the manufacturer's recommended procedures

4. Remove serum using a transfer pipette and transfer:
   a) 1.0 mL into the first 2 mL polypropylene cryovial. (Vial# 1)
   b) 1.0 mL into the second 2 mL polypropylene cryovial. (Vial# 2)
   c) 1.0 mL into the third 2 mL polypropylene cryovial. (Vial# 3)
   d) Transfer any remaining serum into the fourth 2 mL polypropylene cryovial. (Vial# 4)
5. Vial# 1 and vial #2 are the primary samples. Vial #3 and vial #4 are back up samples.
6. Cap the labeled cryovials and freeze the serum samples immediately at approximately -70°C or lower. No more than 1 hour and 45 minutes must be allowed to elapse between collecting blood and freezing the serum sample.
7. If a -70°C freezer is not available, the samples may be stored at approximately -20°C in a commercial grade freezer with no auto-defrost until shipment to selected laboratory in China.

Shipping off Serum Samples for PK Analysis and Immunogenicity Testing for Vedolizumab

To be determined.

Detailed instructions for the handling and shipping of samples are provided in the Study Manual.

Appendix F Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment No. 02 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Clarification for confirmation of entry criteria, including test results.

The primary change occurs in Section 7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

Initial wording:	All entry criteria, including test results, need to be confirmed prior to first dose of study drug on Day 1.
Amended or new wording:	All entry criteria, including test results, need to be confirmed prior to ~~first dose~~ **dosing** of study drug on Day 1.

Rationale for Change:

There is no change to the meaning of the sentence, just to avoid confusion since we only have one dose in the study.

Change 2: Clarification of the in-clinic diet.

The primary change occurs in Section 7.4 Diet, Fluid, Activity Control

Initial wording:	In the clinic, subjects will be provided 3 standard meals and 2 snacks per day, each meal containing approximately 30% fat (relative to the total calories).
Amended or new wording:	In the clinic, subjects will be provided 3 standard meals ~~and 2 snacks~~ per day ~~each meal containing approximately 30% fat (relative to the total calories)~~. **The menu of the standardized meals from the clinical research site needs to be approved by Takeda before the implementation.**

Rationale for Change:

This was revised based on the Site's request per their standard practice for all studies in China

Change 3: Change in definition of timing for significant protocol deviation.

The primary change occurs in 7.5 Section Criteria for Discontinuation or Withdrawal of a Subject

Initial wording:	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.

Amended or new wording:	2. Significant protocol deviation. The discovery after the ~~first dose~~ **dosing** 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.

Rationale for Change:

There is no change to the meaning of the sentence, just to avoid confusion since we only have one dose in the study.

Change 4: Revised Section 8.2 (Investigational Drug Assignment and Dispensing Procedures), to specify that the 3-digit Subject ID number will be used instead of 4-digit enrollment number.

The primary change occurs in Section 8.2 Investigational Drug Assignment and Dispensing Procedures

Initial wording:	~~Subjects will be assigned to receive a 4-digit enrollment number. The number will be assigned by the clinic site personnel in sequential order beginning with 1001. This 4-digit number will be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results. This 4-digit number should only be used for the purposes described in this section. It does not replace the 3-digit subject number which is assigned at the time the informed consent is obtained and which is used for all other procedures to identify the subjects throughout the study.~~
Amended or new wording:	**The 3-digit subject number which is assigned at the time the informed consent is obtained, will be assigned by clinic site personnel in sequential order and which is used for all other procedures to identify the subjects throughout the study, as well as to facilitate the prelabeling of PK samples, contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results.**

Rationale for Change:

To specify that the 3-digit Subject ID number will be used to identify subjects, PK samples, and bioanalytical samples throughout study.

Change 5: Clarify list of serum chemistry laboratory tests.

The primary change occurs in Table 9.a Clinical Laboratory Tests

Initial wording:

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Special
RBCWBC with differential [% and absolute]	ALT	pH	QuantiFERON test for (a)
Hemoglobin	Albumin	Specific gravity	
Hematocrit	Alkaline phosphatase	Protein	
Platelets	AST	Glucose	
PT/INR (b)	Total bilirubin	Blood	
	Direct bilirubin	Nitrite	
	Total protein	Microscopic Analysis	
	Creatinine	(only if positive dipstick	
	Blood urea nitrogen	results):	
	Creatine kinase	RBC/high power field	
	GGT	WBC/high power field	
	Potassium	Epithelial cells, casts etc	
	Sodium		
	Glucose		
	Chloride		
	Bicarbonate		
	Calcium		

Serum	Drug and Alcohol Screen
Serum hCG (c)	Drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine
AVA	
At Screening Only:	Breathalyzer - Alcohol
Hepatitis panel, including HBsAg, HBsAb, HBcAb, anti-HCV and HIV (d)	
FSH (e)	

Amended or new wording:

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Special
RBCWBC with differential [% and absolute]	ALT	pH	QuantiFERON test for (a)
Hemoglobin	Albumin	Specific gravity	
Hematocrit	Alkaline phosphatase	Protein	
Platelets	AST	Glucose	
PT/INR (b)	Total bilirubin	Blood	
	Direct bilirubin	Nitrite	
	Total protein	Microscopic Analysis (only if positive dipstick results):	
	Creatinine		
	Blood ~~urea nitrogen~~ Urea		
	Creatine kinase	RBC/high power field	
	GGT	WBC/high power field	
	Potassium	Epithelial cells, casts etc	
	Sodium		
	Glucose		
	Chloride		
	Bicarbonate or Carbon Dioxide		
	Calcium		

Serum	Drug and Alcohol Screen
Serum hCG (c)	Drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine
AVA	
At Screening Only:	
Hepatitis panel, including HBsAg, HBsAb, HBcAb, anti-HCV and HIV (d)	Breathalyzer - Alcohol
FSH (e)	

Rationale for Change:

Under serum chemistry of clinical laboratory tests to be performed, blood urea can be tested in lieu of blood urea nitrogen and carbon dioxide can be tested as an alternative to bicarbonate.

Change 6: Clarify timing of vital signs.

The primary change occurs in Section 9.1.5 Vital Sign Procedure

Initial wording: Vital signs (temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Check-in (Day -1), Day 1 (predose, and at 1 and 8 hours postdose), Days 2, 8, 10(±1), 15 (±1), 29 (±2), 43(±2), 64 (±3), 85 (±3), 106 (±3), and Final Visit Day 127(±3)/ET. For Days 1 and 2, heart rate and blood pressure will be measured after 5 minutes supine and again at 1 and 3 minutes after standing. For Days 8, 10(±1), 15 (±1), 29 (±2), 43(±2), 64 (±3), 85 (±3), 106 (±3) and Final Visit Day 127(±3)/ET, heart rate and blood pressure will be measured after 5 minutes supine only.

Amended or new wording: Vital signs (temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Check-in (Day -1), Day 1 (predose, and **within ±5 minutes of** 1 hour postdose and **within ±30 minutes** of 8 hours postdose), Days 2, 8, 10(±1), 15 (±1), 29 (±2), 43(±2), 64 (±3), 85 (±3), 106 (±3), and Final Visit Day 127(±3)/ET. For Days 1 and 2, heart rate and blood pressure will be measured after 5 minutes supine and again at 1 and 3 minutes after standing. For Days 8, 10(±1), 15 (±1), 29 (±2), 43(±2), 64 (±3), 85 (±3), 106 (±3) and Final Visit Day 127(±3)/ET, heart rate and blood pressure

	will be measured after 5 minutes supine only.

Rationale for Change:

Several procedures need to be done at specific time points, like vital signs, PK blood sample collection, and ECG at 8h postdose. PK blood sample collection should be the first priority as this is a PK study, so we added a time window for vital signs procedures.

Change 7: Clarification of dosing.

The primary change occurs in Section 9.3.2 Study Entrance

Initial wording:	If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for study entrance, the subject should be assigned to treatment as described in Section 8.2. Subjects will be administered the first dose of study medication in the unit under the supervision of the investigator or designee, as described in Section 8.2.
Amended or new wording:	If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for study entrance, the subject should be assigned to treatment as described in Section 8.2. Subjects will be administered ~~the first~~ **a** dose of study medication in the unit under the supervision of the investigator or designee, as described in Section 8.2.

Rationale for Change:

There is no change to the meaning of the sentence, just to avoid confusion since we only have one dose in the study.

Change 8: Deletion of collection and storage of specimens for genome/gene analysis.

The primary change occurs in 9.4 Biological Sample Retention and Destruction

Initial wording:	In this study, specimens for genome/gene analysis will be collected as described. The genetic material will be preserved and retained for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.
Amended or new wording:	~~In this study, specimens for genome/gene analysis will be collected as described. The genetic material will be preserved and retained for up to but not longer than 15 years or as required by applicable law.~~ The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

Rationale for Change:

This study will not collect specimens for genome/gene analysis nor collect and store such specimens.

Change 9: Correction in approximate blood values to be drawn.

The primary change occurs in Table 9.c Approximate Blood Volume

Initial wording:	The maximum volume of blood at any single day is approximately 59.5 mL, and the approximate total volume of blood for the study is 278.5 mL.
Amended or new wording:	The maximum volume of blood at any single day is approximately ~~59.5~~ **38.5** mL, and the approximate total volume of blood for the study is ~~278.5~~ **276** mL.

Rationale for Change:

The maximum volume of blood at any single day and total volume for the study should be more accurately described as approximately 38.5 mL and approximately 276 mL, respectively.

Change 10: Clarification of timing for when subjects are assessed for signs and symptoms of PML.

The primary change occurs in Section 11.1.1 Risk Minimization Action Program for PML (RAMP Program)

Initial wording:	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.
Amended or new wording:	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.

Rationale for Change:

There is no change to the meaning of the sentence, just to avoid confusion since we only have one dose in the study.

Change 11: Deletion of text regarding samples collected outside the window not being considered a protocol deviation

The primary change occurs in Section 14.2 Protocol Deviations

Initial wording:	Samples collected outside the window will not be considered a protocol deviation.
Amended or new wording:	~~Samples collected outside the window will not be considered a protocol deviation.~~

Rationale for Change:

Original wording was deleted, because collection of samples outside the window is definitely considered a protocol deviation.

Change 12: Modifications to Appendix A (Schedule of Study Procedures) to add Day 8 timepoint for serum pregnancy test (hCG) and Final Visit/ET timepoint for dispensing PML Wallet Card.

The primary change occurs in Appendix A Schedule of Study Procedures

Initial wording:

	Screening		Treatment	Follow up (a)												
Procedures or Observations	**Days -28 to -2**	**Check-in Day -1**	**Day 1**	**Day 2**	**Day 4**	**Day 6**	**Day 8**	**Day 10 (±1)**	**Day 15 (±1)**	**Day 29 (±2)**	**Day 43 (±2)**	**Day 64 (±3)**	**Day 85 (±3)**	**Day 106 (±3)**	**Final Visit Day 127 /ET/ (±3) (b)**	**LTFU Safety Survey Day 168/ (±3)**
Informed consent (c)	X															
Dispense PML wallet card	X															
Serum pregnancy test (hCG) (m)	X	X													X	

Amended or new wording:

	Screening		Treatment	Follow up (a)												
Procedures or Observations	**Days -28 to -2**	**Check-in Day -1**	**Day 1**	**Day 2**	**Day 4**	**Day 6**	**Day 8**	**Day 10 (±1)**	**Day 15 (±1)**	**Day 29 (±2)**	**Day 43 (±2)**	**Day 64 (±3)**	**Day 85 (±3)**	**Day 106 (±3)**	**Final Visit Day 127 /ET/ (±3) (b)**	**LTFU Safety Survey Day 168/ (±3)**
Informed consent (c)	X															
Dispense PML wallet card	X														X	
Serum pregnancy test (hCG) (m)	X	X					X								X	

Rationale for Change:

PML is the major AESI we are monitoring. After receiving the final dose of vedolizumab, all subjects should continue to check for symptoms of PML and inform the doctor if they have any symptoms of PML. The study doctor or nurse will call subjects 6 months after the dose of vedolizumab to ask a few questions about their health. The LTFU PML Wallet Card will not only help the subjects recognize the symptoms of PML but also help regular doctors become familiar with PML reporting process which is part of RAMP.

"X" should also be marked for Day 8 in order to be consistent with the footnote (c) specified under Table 9.2 of the protocol, which states "(c) Serum hCG pregnancy test will be done on all female subjects of childbearing potential at Screening, Check-in (Day -1), Day 8 and at Final Visit Day 127/ET."

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	11-May-2018 17:00 UTC
	Clinical Science Approval	13-May-2018 02:58 UTC
	Biostatistics Approval	14-May-2018 13:46 UTC
	Clinical Pharmacology Approval	14-May-2018 13:53 UTC