Title: A Phase 1, Open-Label, Randomized, Parallel Group Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Autoinjector in Healthy Subjects

NCT Number: NCT03961308

Protocol Approve Date: 11 December 2017

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.

Takeda submitted 3 protocol clarification letters for the final protocol, dated 11-Dec-2017, explaining the discrepancies within the protocol. The clarification letters are appended to the back of the protocol.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1, Open-Label, Randomized, Parallel Group Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Autoinjector in Healthy Subjects

Vedolizumab SC PFS+AI Pharmacokinetic Study

Sponsor:	Takeda Development Center Americas, Inc. One Takeda Parkway, Deerfield, IL 60015		
Study Number:	VedolizumabSC-1022		
IND Number:	118980	**EudraCT Number:**	Not applicable
Compound:	Vedolizumab SC		
Date:	11 December 2017		

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	Contact
Serious adverse event and pregnancy reporting Medical Monitor (medical advice on protocol and study drug) 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 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 are provided 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, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

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

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

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Takeda Development Center Americas, Inc</td><td colspan="2">Compound:
Vedolizumab Injection, for Subcutaneous Use (Vedolizumab SC)</td></tr>
<tr><td colspan="2">Title of Protocol: A Phase 1, Open-Label, Randomized, Parallel Group Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Autoinjector in Healthy Subjects</td><td>IND No.: 118980</td><td>EudraCT No.:
Not applicable</td></tr>
<tr><td colspan="2">Study Number: VedolizumabSC-1022</td><td colspan="2">Phase: 1</td></tr>
<tr><td colspan="4">Study Design:
This is an open-label, randomized, parallel-group study to compare the pharmacokinetics (PK) of a single dose of vedolizumab subcutaneous (SC) 108 mg for injection administered in 2 different device delivery presentations in healthy subjects. A minimum 102 subjects (51 per group) will be randomized to 1 of 2 device presentations (Group A or B).
<table>
<tr><th>Group</th><th>Approximate Number of Subjects</th><th>Treatment Description (a)</th></tr>
<tr><td>A</td><td>51</td><td>Single dose vedolizumab SC 108 mg delivered by prefilled syringe (PFS) (reference).</td></tr>
<tr><td>B</td><td>51</td><td>Single dose vedolizumab SC 108 mg delivered by prefilled syringe in autoinjector (PFS+AI) (test).</td></tr>
</table>
(a) Subjects randomized to each device will also be randomized for the site of administration (abdomen, thigh, or arm). Thus, within each treatment group, there are 3 sites of administration (abdomen, thigh, or arm) randomly assigned, for a total of 6 treatment combinations.
Subjects will be screened up to 28 days to determine eligibility before randomization. Enrolled subjects will return to the clinic at Check-in (Day -1).
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(a) 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.
(b) Subjects will be followed poststudy by telephone to administer a questionnaire, which will include progressive multifocal leukoencephalopathy (PML) questions at Day 168 (±3 days).
Subjects for all treatments groups will be kept in the study unit for at least 24 hours after dosing for safety and PK assessment before discharge. The total confinement period will be 2 days. Subjects will return to the study unit periodically according to the schedule for PK sampling and safety assessments. Subjects will be required to participate in a long-term follow-up safety survey by telephone at Day 168 (±3 days). Subjects who drop out for nonsafety reasons will be replaced at the discretion of the investigator and sponsor.</td></tr>
</table>

Primary Objective:

- To compare the PK of single dose of vedolizumab SC 108 mg administered as PFS vs PFS+AI.

Subject Population: Healthy men and women (nonpregnant and nonlactating).

Number of Subjects:	**Number of Sites:**
Per dose group: 51 Estimated Total: 102 randomized	Estimated total: 1 site in the United States
Dose Level(s):	**Route of Administration:**
Single dose of vedolizumab SC 108 mg	SC injection
Duration of Treatment:	**Period of Evaluation:**
Subject will receive on Day 1 a single dose of vedolizumab SC 108 mg	196 days including Screening Period

Main Criteria for Inclusion:

Healthy male and female (nonpregnant, nonlactating) subjects aged 18 to 65 years, inclusive, with a body mass index from 18 to 28 kg/m² or a body weight >50 kg and <90 kg.

Main Criteria for Exclusion:

- The subject has received any investigational or approved biologic or biosimilar within 30 days or 5 half-lives, of Screening, whichever is longer.
- The subject has had prior exposure to vedolizumab, or has hypersensitivity to vedolizumab or any of its components.
- The subject has had previous exposure to approved or investigational anti-integrins (eg, natalizumab, efalizumab, etrolizumab, AMG 181) or anti- mucosal addressin cell adhesion molecule-1 (MAdCAM-1) antibodies or rituximab.
- Subjects with ≥1 positive responses on the PML subjective symptom checklist at Screening or before dosing on Day 1.
- Subjects with active or latent tuberculosis, regardless of treatment history.

Main Criteria for Evaluation and Analyses:

PK:

Blood samples (5 mL) will be collected for the determination of serum vedolizumab concentrations at the following times: predose (within 30 minutes before the start of SC dosing), 2, 8, 24, 72, 120, and 168 hours after Day 1 dosing, and on Days 10, 15, 29, 43, 64, 85, 106, and Final Visit Day 127/Early Termination.

The following serum PK parameters for vedolizumab SC will be analyzed as primary PK endpoints for each presentation: maximum observed serum concentration (C_{max}), area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}), area under the serum concentration-time curve from time 0 to infinity (AUC_{∞}). Additional PK endpoints include time of first occurrence of C_{max}, and terminal disposition phase half-life.

Safety:

The following safety variables will be used to characterize the safety and tolerability of vedolizumab SC: physical examination findings, treatment-emergent adverse events, clinical laboratory test results (clinical chemistry, hematology, urinalysis), vital sign measurements, and 12-lead electrocardiogram. Percentage of subjects who are positive for antivedolizumab antibodies (AVA) and/or neutralizing AVA.

Statistical Considerations:

PK:

For summary statistics and median plots by sampling time, the nominal PK sampling time will be used; for individual subject plots by time, the actual PK sampling time will be used.

The PK parameters will be summarized descriptively by treatment, by site of administration, and a combination of treatment and site of administration. For AUC_{last}, AUC_{∞}, and C_{max}, individual subject parameters will be plotted by treatment and site of administration within each treatment.

Natural log transformed AUC_{∞} (if data permit), AUC_{last}, and C_{max} will be analyzed using an analysis of covariance model with treatment and site of administration as fixed effect and weight as a continuous covariate. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Single doses of 108 mg of vedolizumab administered as PFS (reference treatment) will be compared vs PFS+AI (Test Treatment). Comparability between the test and reference treatments will be concluded if the 90% CI for C_{max} and AUC_{last} are contained within the range of 0.8 and 1.25.

Sample Size Justification:

The sample size of 51 subjects per group will provide 90% probability of concluding that the ratios of central values for area under the serum concentration-time curve (AUC) or C_{max} between 2 different device presentations is between 0.8 and 1.25. This is assuming that the true difference between the central values is no more than 5% and based on 24% coefficient of variation on AUC or C_{max} from non-Japanese subjects in study MLN0002SC_101. An 18% drop-out rate was assumed for the sample size calculation.

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 vendors identified 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
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
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 quantifiable concentration.
AVA	antivedolizumab antibodies
BMI	body mass index
CD	Crohn's disease
CFR	Code of Federal Regulations
CRF	case report form
C_{max}	maximum observed serum concentration
ECG	electrocardiogram
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
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
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
LFT	liver function test
LTFU	long-term follow-up
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
PFS	prefilled syringe
PFS+AI	prefilled syringe plus autoinjector
PK	pharmacokinetics
PTE	pretreatment event
PML	progressive multifocal leukoencephalopathy
RAMP	Risk Assessment and Minimization for PML

SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
t_{max}	time to first occurrence of C_{max}
UC	ulcerative colitis
ULN	upper limit of normal
VNS	Visual Numeric Scale
WBC	white blood cell

3.4 Corporate Identification

TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Americas, as applicable
Takeda	TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

Vedolizumab (also known as MLN0002, ENTYVIO, or KYNTELES) is a recombinant humanized monoclonal antibody (mAb) composed of 2 light chains of the κ subclass and 2 immunoglobulin G_1 heavy chains that binds specifically to the human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$ integrin is a pivotal mediator of gut immunity and inflammation because of its unique role in mediating the migration of lymphocytes into gut-associated lymphoid tissue and lamina propria, via binding to mucosal addressin cell adhesion molecule-1 (MAdCAM-1). Thus, vedolizumab acts as a gut-selective immunomodulator.

Vedolizumab intravenous (IV) has been developed as a treatment for ulcerative colitis (UC) and Crohn's disease (CD), which are characterized by inflammation of the gastrointestinal tract. Marketing approval has been granted in the United States, European Union, and multiple other countries for the treatment of adult patients with moderately to severely active UC or CD who have failed conventional therapy (ie, corticosteroids or immunomodulators) or tumor necrosis factor alpha antagonists.

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

The bioavailability, pharmacokinetics (PK), and safety of vedolizumab following a single SC injection of vedolizumab SC at 3 dose levels (54, 108, and 160 mg) relative to a single IV infusion of vedolizumab IV 300 mg was examined in a phase 1, open-label study (MLN0002SC_101). Forty-eight (24 Japanese and 24 non-Japanese) healthy, adult male and female subjects were randomized. A total of 12 subjects received a single dose of vedolizumab IV 300 mg and 36 subjects received a single dose of vedolizumab SC at 54, 108, or 160 mg (12 subjects per dose group). The bioavailability estimate from vedolizumab SC was 75.1%. The SC bioavailability was independent of the SC doses evaluated (54, 108, and 160 mg vedolizumab SC). All other PK parameters estimates were very similar to the values derived from phase 3 data with vedolizumab IV, and there were no PK differences by race (Japanese vs non-Japanese). In study MLN0002SC_101, 75.0% of subjects (36 of 48 subjects) had treatment-emergent adverse events (TEAEs). The percentage of subjects with a TEAE was the same when comparing subjects who received vedolizumab SC and subjects who received vedolizumab IV. All TEAEs were considered by the investigator to be mild or moderate in intensity; no TEAEs of severe intensity were reported. Four subjects had persistently moderate to high antivedolizumab antibodies (AVA) titers

for ≥14 weeks with an impact on PK; these subjects were excluded from population PK analysis and were not included in the noncompartmental PK summaries. Overall, vedolizumab SC and vedolizumab IV were well tolerated in this study. The observed TEAEs were consistent with the overall safety profile of vedolizumab.

Previously conducted clinical studies have characterized the efficacy, safety, tolerability, PK, pharmacodynamics, and immunogenicity of vedolizumab IV, a lyophilized formulation. 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.

4.2 Rationale for the Proposed Study

IV infusion may not be convenient as long-term therapy, vedolizumab SC has been developed to ultimately enable injection of vedolizumab by patients or their caregivers. The safety and efficacy of this formulation is currently being investigated in ongoing phase 3 studies in adults with moderately to severely active UC or CD who achieved clinical response following open-label vedolizumab IV therapy (MLN0002SC-3027 and MLN0002SC-3031). The current presentation of the SC formulation is in a prefilled syringe.

The main purpose of this phase 1 clinical study is to compare the PK of a vedolizumab SC 108 mg dose in a prefilled syringe (PFS) vs prefilled syringe in autoinjector (PFS+AI). The PFS+AI presentation is planned to be commercially available device after approval.

4.3 Benefit/Risk Profile

The proposed study (VedolizumabSC-1022) is designed to evaluate the PK and variability of a vedolizumab SC 108 mg dose in a PFS vs PFS+AI. No changes were made to the vedolizumab SC drug product composition that would impact the primary structure of the protein, and comparable biochemical properties and in vitro functional activity have been demonstrated. Therefore, the nonclinical and clinical information from studies with vedolizumab IV are considered relevant.

The safety of the vedolizumab SC presentation is expected to be similar to that of vedolizumab IV because of similar exposure, outside of expected local administration site events, such as injection-site reactions. The observed adverse events (AEs) with vedolizumab SC are consistent with the vedolizumab IV safety profile in ongoing phase 3 clinical studies.

A phase 1 single dose study with the SC formulation in health volunteers was conducted and identified no safety concerns. This study is comparing different devices and the safety is expected to be similar among these devices.

Overall, vedolizumab has been well tolerated in clinical studies, including a phase 1 study of vedolizumab SC.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To compare the PK of single dose of vedolizumab SC 108 mg administered as PFS vs PFS+AI.

5.1.2 Additional Objectives

- To evaluate the safety and tolerability of single dose of vedolizumab SC 108 mg administered as PFS and PFS+AI.
- To evaluate the development of AVA and neutralizing AVA following single dose of vedolizumab SC 108 mg administered as PFS and PFS+AI.
- To evaluate the PK of single dose of vedolizumab SC 108 mg administered at 3 different sites (arm, abdomen, and thigh).

5.2 Endpoints

5.2.1 Primary Endpoints

The following serum PK parameters will be analyzed for each presentation following a single dose of vedolizumab SC:

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

5.2.2 Additional Endpoints

5.2.2.1 Safety Endpoints

The following safety variables will be used to characterize the safety and tolerability of vedolizumab SC:

- Physical examination findings, TEAEs, clinical laboratory test results, vital sign measurements, and 12-lead electrocardiograms (ECG).
- Percentage of subjects who are positive for AVA during the study.
- Percentage of subjects who have positive neutralizing AVA during the study.

5.2.2.2 PK Endpoints

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

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is an open-label, randomized, parallel-group study to compare the PK of a single dose of vedolizumab SC 108 mg for injection administered in 2 different device delivery presentations in healthy subjects. A minimum 102 subjects (51 per group) will be randomized to 1 of 2 device presentations (Group A or B).

A summary of the treatment groups is presented in Table 6.a.

Table 6.a Summary of Treatment Groups

Group	Approximate Number of Subjects	Treatment (a)
A	51	Single dose of vedolizumab SC 108 mg delivered by PFS (reference).
B	51	Single dose of vedolizumab SC 108 mg delivered by PFS+AI (test).

(a) Subjects randomized to each device will also be randomized for the site of administration (abdomen, thigh, or arm). Thus, within each treatment group, there are 3 sites of administration (abdomen, thigh, or arm) randomly assigned, for a total of 6 treatment combinations. Seventeen subjects will be allocated to each site of administration within each treatment.

Subjects will be screened up to 28 days to determine eligibility before randomization. Eligible subjects will return to the clinic at Check-in (Day -1). On Day 1, all doses will be administered by a health care professional. 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="5">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</td><td>Days
3-8</td><td>Days 10, 15, 29, 43, 64, 85, 106</td><td>Final Visit/ Early Termination Day 127 (a)</td><td>Day 168 Follow-up Phone Call (b)</td></tr>
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</table>

(a) 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.
(b) Subjects will be followed poststudy by telephone to administer a questionnaire, which will include progressive multifocal leukoencephalopathy (PML) questions at Day 168 (±3 days).

Subjects for all treatments groups will be kept in the study unit from Day -1 Check-in until at least 24 hours after dosing (Day 2) for safety and PK assessment before discharge. The minimum confinement will be 2 nights (Days -1 to 2, inclusive). Subjects can stay longer in the clinic at the discretion of the investigator. Subjects will return to the study units periodically according to the

schedule for PK sampling and safety assessments. Subjects will be required to participate in a long-term follow-up (LTFU) safety survey by telephone on Day 168.

At least 40% of each sex group will be enrolled.

6.2 Justification for Study Design, Dose, and Endpoints

This study is designed in accordance with Food and Drug Administration (FDA) Guidance documents [1,2]. The primary PK endpoints C_{max} and area under the serum concentration-time curve (AUC) are standard parameters to compare the rate and extent of absorption.

This study will be performed in healthy subjects, rather than the target subject population (ie, patients with UC or CD) because of the potential for immunogenicity in subjects after single dose administration. Similar PK has been observed in healthy subjects and patients with UC or CD following administration of vedolizumab IV.

The study design is open-label, since the primary objective is to assess objective variables, that is, vedolizumab PK using multiple device presentations. Because this is an objective measurement, there is consequently no risk of potential bias of the study results; hence, neither study blinding nor inclusion of a placebo group is required.

Vedolizumab is a mAb with a long half-life that precludes a crossover design. Therefore, a parallel design will be used.

Vedolizumab SC dose of 108 mg was selected for this study as it is the dose being tested in phase 3 vedolizumab SC studies.

AEs, vital signs, weight, ECG findings, and laboratory test results are commonly used safety endpoints.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

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

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

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before randomization or first dose or other.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria before 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 before the initiation of any study procedures including requesting that a subject fast for any laboratory evaluations.
3. The subject is a healthy male or female (nonpregnant and nonlactating) adult aged 18 to 65 years, inclusive, at the time of informed consent.
4. The subject weighs >50 kg and <90 kg or has a body mass index (BMI) from 18 to 28 kg/m^2, inclusive, at the time of informed consent.
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 and for 18 weeks after the 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 for 18 weeks after the dose.

* Definitions and highly effective methods of contraception are defined in Section 9.1.9 and reporting responsibilities are defined in Section 9.1.10.

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 had previous exposure to approved or investigational approved biologic or biosimilar agent within 30 days or 5 half-lives of Screening.
2. The subject has had previous exposure to approved or investigational anti-integrins (eg, natalizumab, efalizumab, etrolizumab, AMG 181) or anti-MAdCAM-1 antibodies or rituximab.
3. The subject has had previous exposure to vedolizumab.
4. The subject has had hypersensitivity or allergies to any of the vedolizumab excipients.
5. The subject has a history of allergic or anaphylactic reaction to any therapeutic or diagnostic mAb or molecules made of components of mAb.

6. The subject has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease.
7. The subject has 1 or more positive responses on the PML subjective symptom checklist at screening or before dosing on Day 1.
8. The subject has any of the following laboratory abnormalities during the Screening Period:
   a) Hemoglobin level <8 g/dL.
   b) White blood cell (WBC) count $<3\times10^9$/L.
   c) Lymphocyte count $<0.5\times10^9$/L.
   d) Platelet count $<100\times10^9$/L or $>1200\times10^9$/L.
   e) Alkaline phosphatase >3×upper limit of normal (ULN).
   f) Serum creatinine >2×ULN.
9. The subject has a positive urine drug result for drugs of abuse (defined as any illicit drug use) at Screening or Check-in (Day -1).
10. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year before the Screening Visit or is unwilling to agree to abstain from alcohol for 7 days before Day -1 throughout confinement and for 48 hours before each clinic visit; and drugs throughout the study.
11. The subject has taken any excluded medication or supplements during the time periods listed in Table 7.a.
12. If female, the subject is lactating or has a positive serum pregnancy test during the Screening Period or a positive serum pregnancy test at Check-in (Day -1), before study drug administration.
13. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 18 weeks after participating in this study; or intending to donate ova during such time period.
14. If male, the subject intends to donate sperm during the course of this study or for 18 weeks thereafter.
15. 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 participant'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 this study. This includes, but is not limited to, peptic ulcer disease, seizure disorders, and cardiac arrhythmias.

16. 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.
17. The subject has a history of cancer, except basal cell carcinoma that has been in remission for at least 5 years before Day 1.
18. The subject has evidence of an active infection during the Screening Period.
19. The subject has received any live vaccinations within 30 days before Screening.
20. The subject has 1 of the following at Screening:
    a) Chronic hepatitis B virus infection: positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody, or
    b) Chronic hepatitis C virus (HCV) infection: all subjects who tested positive for HCV antibody which is confirmed with a positive HCV RNA viral load test (those treated and cured for HCV infection are allowed).
21. The subject has active or latent tuberculosis (TB) as evidenced by the following:
    a) A diagnostic TB test performed within 30 days of Screening or during the Screening Period that is positive, defined as:
       – Positive QuantiFERON test or 2 successive indeterminate QuantiFERON tests, OR
       – A TB skin test reaction ≥5 mm.
         NOTE: If subjects have received BCG vaccine then a QuantiFERON TB Gold test should be performed instead of the TB skin test.

       Note: Subjects with documented previously treated TB with a negative QuantiFERON test can be included in the study.
22. The subject has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
23. The subject has poor peripheral venous access.
24. The subject is unable to attend all the study visits or comply with study procedures.
25. The subject has donated or lost 450 mL or more of his or her blood volume (including serum pheresis), or had a transfusion of any blood product within 45 days before Day 1.
26. 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 or designee.
27. The subject has abnormal Screening or Check-in (Day -1) laboratory values that suggest a clinically significant underlying disease or subject with the following laboratory abnormalities: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5 times the ULN.

28. 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.

7.3 Excluded Medications, Supplements, Dietary Products

Use of the agents in Table 7.a is prohibited from the time points specified until collection of the last PK sample.

Table 7.a Prohibited Medications and Supplements

28 days before Check-in (Day -1)	7 days before Check-in (Day -1)
Prescription medications	Vitamin supplements
OTC medications (a)	
All live vaccines, except for inactivated influenza vaccine	

OTC=over-the-counter.
(a) Occasional use of acetaminophen/paracetamol (≤1 g/day) or other medication as approved by Takeda on a case-by-case basis is 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. Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

Subjects will abstain from the use of tobacco or nicotine-containing products before dosing and during confinement in the research unit.

7.4 Diet, Fluid, Activity Control

The meals served on the day of dosing should be identical for each cohort (if subject is enrolled in cohort) in the study. The study menu should be recorded and submitted to the study file with a copy provided to the sponsor before the start of the study.

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

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form (CRF) using the following categories. For screen failure subjects, refer to Section 9.1.15.

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 drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.8), if the following circumstances occur at any time during study drug treatment:

  – ALT or AST >8×ULN, or

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

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

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

2. Significant protocol deviation. The discovery after the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documentation.
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 CRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal because of an AE should not be recorded in the "voluntary withdrawal" category).
5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.
7. Other.

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

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 Early Termination Visit. Discontinued or withdrawn subjects will be replaced at the discretion of the investigator and the sponsor.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

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

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

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

8.1.1.1 Vedolizumab SC in PFS

The study sites will be supplied with the following medication in an open-label manner: liquid vedolizumab SC 108 mg/CCI in single-use bare glass PFS with finger flange (PFS). Each PFS will be labeled and packaged in a single plastic tray with sealed lidding and individually packed into a folding box or carton.

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

8.1.1.2 Vedolizumab SC in Autoinjector

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

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

8.1.2 Storage

All clinical trial material must be kept in an appropriate, limited-access, secure location until it is used or returned to the sponsor or designee for destruction. All study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

Vedolizumab SC must be stored in a refrigerator at a temperature between 2°C to 8°C (36ºF to 46ºF). Do not freeze. Retain in original package to protect from light. The investigator should ensure that study medication is used only in accordance with the approved protocol. Study medication will be dispensed only for subjects enrolled in the study.

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 principal investigator or designee as indicated in Table 8.a.

Table 8.a Dose and Regimen

Group	Dose	Treatment Description (a)
A	vedolizumab SC 108 mg	Single dose delivered by PFS (reference).
B	vedolizumab SC 108 mg	Single dose delivered by PFS+AI (test).

(a) Within each treatment group, there are 3 sites of administration (arm, abdomen, or thigh) randomly assigned, for 6 treatment combinations total.

Detailed instructions for SC administration of vedolizumab with the PFS and PFS+AI will be provided to the study site(s) in a separate Instructions for Use and Medication Guide.

8.1.4 Overdose

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

Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

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

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will be assigned, in the order in which they are randomized into the study, to receive their treatment and site of administration according to the randomization schedule allocated to the site. The randomization sequence number will be entered onto the CRF.

Subjects will be assigned to receive a 4-digit randomization sequence number on Day 1. The number will be assigned by the clinic site personnel in sequential order. There will be equal assignment of the subjects to 1 of the 6 possible combinations of 2 treatments and 3 administration sites. Male subjects will be assigned a randomization sequence number in ascending order; female subjects will be assigned a randomization sequence number in descending order.

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.

8.3 Randomization Code Creation and Storage

The final randomization list will be created, reviewed, and approved by CCI Randomization and Unblinding Administrators who are not members of the study team. After the final randomization lists have been approved, the randomization lists will be transferred to the CCI Pharmacy and kept in a restricted area to which only the CCI Pharmacy staff has access.

8.4 Accountability and Destruction of Sponsor-Supplied Drugs

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

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

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

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

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the lot/medication identification/job 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 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, and the date and amount returned to the site by the subject, including the initials, seal, or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All used devices must be returned intact (not destroyed) to Takeda or designee.

Before 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 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.

In the event of expiry date extension of supplies already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

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

8.5 Reserve Study Medication Samples for Retention

The investigator will retain a reserve sample (5 times the amount required for full analytical release testing) of study drug in accordance with FDA regulations. The investigator or the investigator's designee will select the appropriate number of containers of study drug for retention, as specified in the bioretention letter to be provided by Takeda Clinical Supplies. Reserve samples will be stored under conditions consistent with the product's labeling and in a segregated area with access limited to authorized personnel. Each reserve sample will be retained for a period of at least 5 years following the date the application or supplemental application is approved by the FDA. If the application is not approved, regulations specify that these samples must be stored for at least 5 years following the date of completion of this bioavailability study. The clinical site should not dispose of the reserve samples without written authorization from Takeda. If at any time the investigator is unable to comply with these requirements, the investigator should immediately notify Takeda regarding arrangements for storing reserve samples and associated study records on the investigator's behalf.

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 before 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 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, Hispanic ethnicity, 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 resolved at or before 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 14 days before signing of informed consent.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment before first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as not clinically significant or clinically significant by the investigator and recorded in the source document and CRF. All clinically significant findings/changes will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate CRF described in Section 10.0 or Section 9.1.7.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately before the start of the study drug must be assessed as not clinically significant or clinically significant by the investigator and recorded in the source document and CRF. Any clinically significant change or new diagnosis as a result of a clinically

significant change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE CRF described in Section 10.0.

9.1.4 Weight, Height, and BMI

Body weight and height will be obtained with the subject's shoes off and jacket or coat removed.

BMI equals a person's weight in kilograms divided by height in meters squared (BMI=kg/m^2). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 rounded down and 0.5 to 0.9 rounded up.

9.1.5 Vital Sign Procedure

Vital signs will include body temperature (oral measurement), respiratory rate, sitting/standing blood pressure (systolic and diastolic, resting more than 5 minutes), and pulse (beats per minute).

Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Check-in (Day -1), Day 1 (predose, postdose), Days 8, 106±3, and Final Visit Day 127±3/Early Termination. For Day 1, heart rate and blood pressure will be measured after 5 minutes in the supine position and at 1 and 3 minutes after standing. For Days 8, 106±3, and 127±3/Early Termination, heart rate and blood pressure will be measured after 5 minutes supine only.

All measurements will be recorded on the source documents and in the CRF.

Vital signs should be measured at the same time of the day across visits if possible. When vital signs are scheduled at the same time as blood draws, vital signs will take priority and will be obtained within approximately 5 minutes before the scheduled blood draw.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the CRF. 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, according to the judgment of the investigator. 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. With the exception of the Screening Visit, laboratory samples will be taken following a minimum 10-hour

overnight fast before collection 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
RBC WBC with differential Hemoglobin Hematocrit Platelets PT/INR (a)	ALT Albumin Alkaline phosphatase AST Total bilirubin Direct bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium	pH Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis* (only if positive dipsticks results): RBC/high power field WBC/high power field Epithelial cells, casts etc *To be performed if abnormal (Verify with PV MD and Medical Monitor)	QuantiFERON test (b)

Diagnostic Screening:	
Serum	**Drug and Alcohol Screen**
Female subjects only hCG (for pregnancy) (c) **At Screening Only:** HIV test Hepatitis panel, including HBsAg and anti-HCV FSH if menopause is suspected (d)	Drug screen (urine), including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates Alcohol (breathalyzer/urine)

FSH=follicle-stimulating hormone, GGT=γ-glutamyl transferase, hCG=human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cell.
(a) Prothrombin time/INR to be performed at Screening and Final Visit Day 127/Early Termination.
(b) Performed at Screening only. All subjects must have documented evidence of a negative QuantiFERON test at Screening. Initial indeterminate results will be repeated; a subject with 2 indeterminate results will be excluded.
(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/Early Termination.
(d) FSH level will be obtained for female subjects at Screening if they are postmenopausal by history (ie, 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) and not surgically sterile. The FSH result must be >40 IU/L for the subject to be permitted not to use adequate contraception.

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 to 72 hours after the abnormality was noted. (Refer to Section 7.5 and Section 10.2.3 for the appropriate guidance on reporting abnormal liver function tests.)

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

All laboratory safety data will be transferred electronically to Takeda or designee in the format requested by Takeda. If the laboratory is unable to electronically transfer data, the investigator or designee is responsible for transcribing or attaching laboratory results to the CRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the principal investigator or designee indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified before the first dose will require clear and complete documentation in the source documents as to the investigator's assessment of not clinically significant before proceeding with enrollment/randomization.

All clinically significant laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate CRF. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.9 Contraception and Pregnancy Avoidance Procedure

9.1.9.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study drug, 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.

9.1.9.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective method of contraception (from the list below).

In addition they must be advised not to donate ova during this period.

9.1.9.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

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

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

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the acceptable methods of contraception are:
    - Nonhormonal Methods:
        - Intrauterine device.
        - Bilateral tubal occlusion.
        - Vasectomized partner (provided that partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical assessment of the surgical success.
        - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month before the first dose until 18 weeks after last dose.
    - Hormonal Methods: Hormonal contraception may be susceptible to interaction with the investigative compound, comparator, concomitant medications, which may reduce the efficacy of the contraception method.
        - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months:
            - Oral.
            - Intravaginal (eg, ring).

- Transdermal.

– Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months:

- Oral.
- Injectable.
- Implantable.

2. Subjects will be provided with information on highly effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
3. During the course of the study, regular serum hCG pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) Contraceptive requirements of the study.
   b) Reasons for use of barrier methods (ie, condom) in men with pregnant partners.
   c) Assessment of subject compliance through questions such as:
      – Have you used the contraception consistently and correctly since the last visit?
      – Have you forgotten to use contraception since the last visit?
      – Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is “yes”)
      – Is there a chance you could be pregnant?
4. In addition to a negative serum hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative serum hCG pregnancy test as close as possible and before first dose of study medication, preferably on the same day.

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 SC) 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 drug, for example, after Day 1 or within 18 weeks of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

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 female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All reported pregnancies, including female partners of male subjects, 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

Standard 12-lead ECGs will be recorded at Screening, Check-in (Day -1), Day 1 (predose [within 0.5 hours before dosing the SC injection]) and Final Visit Day 127/Early Termination. When an ECG recording is scheduled for the same day as blood draws (eg, PK or AVA sampling), the ECG recording will be collected 5 minutes before the nominal time of the blood sample.

Additional unscheduled ECGs may be recorded where clinically necessary for subject safety.

ECGs will be read automatically and also, the investigator or subinvestigator 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, QT interval with Fridericia correction method and QT interval with Bazett correction method 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 CRF. 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 the assessment of AVA will be collected as shown in the Schedule of Study Procedures (Appendix A). A sample will be assessed for neutralizing AVA if AVA is detected. If a subject experiences an SAE, a blood sample for AVA assessment should be obtained at the unscheduled visit.

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

Instructions for sample processing and shipment are provided in the Laboratory Manual.

9.1.13 PK Sample Collection

9.1.13.1 Collection of Serum for PK Sampling

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

PK samples should be collected as specified in Table 9.b even if the vedolizumab SC is discontinued before the complete dose is administered to the subject.

Table 9.b Collection of Blood Samples for PK Analysis

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
Vedolizumab	Serum	1	Within 0.5 hours before the SC injection (predose), 2, 8, 24, 72, 120, and 168 hours after Day 1 dosing, and on Days 10, 15, 29, 43, 64, 85, 106, and Final Visit Day 127/Early Termination (a)

(a) If a subject experiences an SAE, a blood sample for PK analysis should also be obtained at the unscheduled visit. PK samples will be collected at Early Termination at the discretion of the investigator.

The actual date and time of sample collection will be recorded on the source document and CRF. Samples collected 10% from the nominal time will not be considered a protocol deviation as long as the exact date and time of PK sampling collection is recorded in the CRF.

9.1.13.2 Bioanalytical Methods

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

9.1.14 PK Parameters

The PK parameters of vedolizumab will be determined from the concentration-time profiles for all evaluable subjects using a noncompartmental analysis method. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be calculated for serum concentration values of vedolizumab:

Symbol/Term	Definition
Serum	
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. A more detailed description will be provided in the clinical pharmacology analysis plan.

9.1.15 TB 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, Wallet Card, and Follow-up Phone call

Clinic 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 before dose, Day 127 (±3)/Early Termination Visit, and at any unscheduled visits.

A wallet card that denotes key study information, including signs and symptoms of PML, will be distributed to all subjects during Screening.

Upon completion or early termination from the study, all subjects will be required to participate by telephone in a LTFU safety survey on Day 168. A questionnaire will be administered and will include PML and neurological symptom question. Any subjects reporting signs and/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 for PML (RAMP) algorithm. The PML checklists and the RAMP algorithm and tools are included in a separate manual. All confirmed cases of PML will be recorded as SAEs.

9.1.17 Pain Scale Assessment

The Visual Numeric Scale (VNS) [3] for self-reported pain assessment at the injection site will be completed by each subject. The VNS will be completed on Day 1 immediately following the SC injection and a second assessment will be performed between 15 and 30 minutes following the injection. Subjects will be presented with the pain scale and instructed to assess their pain on a scale of 0 to 10, with 0=no pain and 10=severe pain.

9.1.18 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If a subject is withdrawn at the screening visit, the investigator should complete the CRF screen failure form.

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

- PTE/AE.
- Screen failure (did not meet entrance criteria).
- Protocol deviation.
- Lost to follow-up.
- Withdrawal by subject.
- Study terminated by sponsor.

- Death.

Subject identification 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.

9.1.19 Documentation of Randomization

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

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

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 CRFs. An inventory of the study drug 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 before the first dose of study medication. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.18 for procedures for documenting screening failures.

9.3.2 Randomization

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized as described according to the randomization schedule. Subjects will be administered 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 9.1.18.

9.3.3 Final Visit or Early Termination

A final visit will be scheduled 127 (±3) days after the dose of study drug or at the Early Termination Visit. For all subjects receiving study drug, the investigator must complete the End of Study CRF page.

The reason for discontinuation must be documented in the source document and CRF. For all subjects receiving study medication, the investigator must complete the End of Study CRF page.

9.3.4 Follow-up

Follow-up will begin after the last dose of study drug and will continue for 18 weeks (ie, Day 127±3 days) thereafter.

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

9.4 Blood Volume

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

Table 9.c Approximate Blood Volume

Sample Type	Sample Volume (mL)	Number of Samples		Total Volume (mL)
		Screening and Day -1	Days 1 to 127	
Clinical laboratory tests (Screening)	20 mL	1	NA	20
Clinical laboratory tests (Nonscreening)	10 mL	1	4	50
AVA assessment	8.5 mL	0	6	51
PK blood collection	5 mL	0	15	75
Total Approximate Blood Sampling Volume				**196**

NA=not applicable.

The maximum volume of blood planned at any single day is approximately 38.5 mL, and the approximate total volume of blood for the study is 196 mL.

Total blood volume collections for the study may increase if additional assessments are needed for AE/SAE occurrence, or at the investigators discretion.

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 before administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses 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 findings are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding is 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) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a pre-existing degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

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

Changes in intensity of AEs/serious PTEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) because of a worsening of the pre-existing condition, the

worsening of the condition should be recorded as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

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

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 CRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the CRF.

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

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

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 AEs of Special Interest

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

10.1.6 Intensity of PTEs and AEs

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

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

10.1.7 Relationship of AEs to Study Drug(s)

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

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

10.1.8 Relationship to Study Procedures

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

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

10.1.9 Start Date

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

10.1.10 Stop Date

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

10.1.11 Frequency

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

10.1.12 Action Concerning Study Drug

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

10.1.13 Outcome

- Recovered/resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (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 because of 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 drug (Day 1) or until screen failure. For subjects who discontinue before study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study drug (Day 1). Routine collection of AEs will continue until the Final Visit (Day 127±3 days).

10.2.1.2 PTE and AE Reporting

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

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

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

10.2.1.3 AEs of Special Interest

If these special interest AEs, which occur during the treatment period or the follow-up period, are considered to be clinically significant based on the criteria below, they should be recorded in a special interest AE CRF or an SAE form. The SAE form should be completed and reported to the SAE reporting contact in Section 1.0 within 24 hours.

Hypersensitivity Reactions (Including Injection Site Reactions)

Currently, there is no evidence to support the routine prophylactic administration of premedication (eg, antihistamines, corticosteroids) to subjects receiving vedolizumab; hence, such premedications are unlikely to be necessary or beneficial.

Vedolizumab SC will be administered by a healthcare professional, who should be prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measure should be available for immediate use. Subjects should be observed during the SC administration and for 2 hours following completion of the administration.

Subjects will be instructed to report the development of rash, hives, pruritus, flushing, urticaria, injection site pain, redness and/or swelling, etc, that may represent an administration-related reaction to study medication. Subjects will be asked to report administration-related AEs to the sites immediately as they are experienced or after having received appropriate medical care. Appropriate treatment and follow-up will be determined by the investigator. If signs or symptoms of an administration-related reaction are observed during the administration of study medication, it should

be immediately discontinued and the subject treated as medically appropriate. Subjects with a severe or serious administration-related reaction (eg, shortness of breath, wheezing, stridor, angioedema, life-threatening change in vital signs, severe injection site reactions) must be withdrawn from the study (see Study Manual).

Any injection site reaction will be collected and graded as follows:

Grade 1: Tenderness with or without associated symptoms (eg warmth, erythema, itching).

Grade 2: Pain, lipodystrophy, edema, phlebitis.

Grade 3: Ulceration or necrosis, severe tissue damage, operative intervention indicated.

Grade 4: Life threatening consequences; urgent intervention indicated.

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

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

The SAE 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 LFTs

If a subject is noted to have ALT or AST elevated >3×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases CRF 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 CRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.1).

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, 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 the study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the study. The study site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with local 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 Assessment and Minimization for PML

To address the hypothetical risk of the development of PML in patients treated with vedolizumab, the sponsor, with input from renowned PML experts, has developed the RAMP program. The complete description of the RAMP program, including materials and instructions for its implementation and monitoring, is included in a separate manual. The RAMP is focused on early clinical detection and management of PML, including the discontinuation of study drug, if applicable. Subjects are assessed for signs and symptoms of PML before 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). An IAC has been established as part of the RAMP program to review new neurological signs and symptoms potentially consistent with PML, and will provide input regarding patient evaluation and management as defined in the IAC charter.

To ensure the 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 patients about PML and the RAMP procedures will be distributed to the site. Formal teaching and training will be performed for site personnel before the start of the study. Subjects will receive training and educational materials before receiving treatment. The informed consent form will contain specific information on the hypothetical risk of PML. The PML IAC will be informed of all new neurological signs and symptoms potentially consistent with PML per the PML Case Evaluation Algorithm and will review the individual subject data. The algorithm and tools are included in the Study Manual. All documented cases of PML will be reported as SAEs, 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 medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 CRFs (Electronic and Paper)

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

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

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

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

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

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

12.2 Record Retention

The investigator 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 CRFs, 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 study site agreement between the investigator and sponsor.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

A targeted review will be conducted before 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.

PK 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 by treatment, and by treatment and site of administration. 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, sex, ethnicity, and race).

13.1.3 PK Analysis

Concentrations will be listed and summarized descriptively by PK sampling time. Summary will be done by treatment, and by treatment and site of administration. Individual subject and median profiles of the concentration-time data will be plotted by treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time will be used.

PK parameters will be summarized descriptively by treatment, by site of administration, and by treatment and site of administration. For AUC and C_{max}, individual subject parameters will be plotted by treatment and site of administration within each treatment.

Natural log transformed AUC_{∞} (if data permit), AUC_{last} and C_{max} will be analyzed using an analysis of covariance model with treatment and site of administration as a fixed effect and weight as a continuous covariate. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric

means (Test/Reference) and 90% CIs for the ratios. Single doses of 108 mg of vedolizumab administered as PFS (reference treatment) will be compared vs PFS+AI (test treatment). Comparability between the test and reference treatments will be concluded if the 90% CIs for C_{max} and AUC_{last} are contained within the range of 0.8 and 1.25.

Additional statistical analyses may be performed if deemed appropriate.

A more detailed description of the planned analyses will be presented in the SAP.

13.1.4 Safety Analysis

For all safety summary tables stated under this section, the tables will be summarized by treatment, by site of administration, and by treatment and site of administration for all subjects. AEs will be summarized using the safety analysis set.

All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class.

The number and percentage of subjects with TEAEs, defined as any AEs, regardless of relationship to study drug, AESIs for vedolizumab (ie, PML, liver injury, injection site reactions), and SAEs, which occur on or after dosing in subjects, will be summarized by MedDRA system organ class, and preferred term, by severity, and by relationship to study drug. Separate summaries will also be generated for AEs by treatment-related and 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.

Data from the LTFU survey will be summarized descriptively.

VNS pain scale assessment data will be summarized.

The proportion of subjects with positive AVA and proportion of subjects with positive neutralizing AVA during the study will be summarized at each visit.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

The sample size of 51 subjects per group would provide 90% probability of concluding that the ratios of central values for AUC or C_{max} between 2 different device presentations is between 0.8 and 1.25. This is assuming that the true difference between the central values is no more than 5% and based on 24% coefficient of variation on AUC or C_{max} from non-Japanese subjects in study MLN0002SC_101. An 18% drop-out rate was assumed for the sample size calculation.

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 CRFs. Source documents are defined as original documents, data, and records. The investigator and study site guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC

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

14.2 Protocol Deviations

The investigator 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. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

However, blood samples not collected within the interval specified for the scheduled sample time should be reported to Takeda using the Protocol Deviation Form.

Protocol Deviation Forms are to be completed for PK samples collected outside 10% of nominal time without date and time of collection.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare

products Regulatory Agency, 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 study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members because of 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 once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification no protocol activities, including screening may occur. Study 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 before 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 before 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 before 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 trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

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

15.4.2 Clinical Trial Registration

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

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

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

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

1. Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations. US Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). March 2003. Publication No. 5356.
2. Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). May 2014.
3. Stanford Patient Education Research Center. Pain Visual Numeric. Stanford School of Medicine. Accessed 09 January 2014. Available at: http://patienteducation.stanford.edu/research/vnspain.pdf.

Appendix A Schedule of Study Procedures

Procedures or Observations	Screening		Treat-ment	Follow-up (a)													Unscheduled Visit
	Days -28 to -2	Check-in Day -1	Day 1	Day 2	Day 4±1	Day 6±1	Day 8±1	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±3 / ET	Follow-up Phone Call Day 168±3	
Informed consent (b)	X																
Inclusion/exclusion criteria	X	X															
Demographics and medical history	X																
Medication history	X																
TB screening (c)	X																
PML checklist (d)	X		X												X		X
Dispense PML wallet card (d)	X																
LTFU questionnaire																X	
Physical examination (e)	X	X	X				X			X					X		
Vital signs (f)	X	X	X												X		
Height, weight, and BMI (g)	X	X												X			
Concomitant medications (h)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concurrent medical conditions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG (i)	X	X	X												X		
Laboratory evaluations (j)	X	X					X			X			X		X		
Urine drug screen	X	X															
Alcohol screen (breathalyzer/urine)	X	X															
PT/INR	X														X		
Serum pregnancy test (hCG) (k)	X	X													X		
FSH (l)	X																
HBsAg, Anti-HCV, and HIV	X																
Confinement (m)		X	X	X													
Administration of study drug			X														
Pain assessment (n)			X														
AVA assessment (o)			X							X		X	X	X	X		X
PK blood collection (p)			X	X	X	X	X	X	X	X	X	X	X	X	X		X
PTE/AE assessment (q)	X	X	X ----------X														X

Footnotes are on the next page.

ET=Early Termination, PT=prothrombin time.
(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 have a ±3 day window.
(b) Informed consent must be signed before any study-specific procedures are performed.
(c) All subjects must have a negative QuantiFERON test at Screening. Initial indeterminate results will be repeated; a subject with 2 indeterminate results will be excluded.
(d) The PML checklist is administered at Screening, on Day 1 before the administration of study drug, and 127±3/ET, and at any unscheduled visits. A wallet card that denotes key study information, including signs and symptoms of PML, will be distributed to all subjects at Screening.
(e) A physical examination will be performed at Screening, on Days -1, 1, 8, 29, and at the Final Visit Day 127/ET. All physical examinations will be performed by the investigator or subinvestigator. Clinically significant findings on the physical examination that occur after dosing with study drug will be recorded as AEs.
(f) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Check-in (Day -1), Day 1 (predose, postdose), and Final Visit Day 127±3/ET. For Day 1, heart rate and blood pressure will be measured after 5 minutes in the supine position and at 1 and 3 minutes after standing. For Day 127±3/ET, heart rate and blood pressure will be measured after 5 minutes supine only.
(g) Height and weight will be measured and BMI will be calculated at Screening. Weight will also be measured at Check-in Day -1 and Day 106±3.
(h) All ongoing medications from Screening through Final Visit Day 127/ET will be recorded.
(i) Standard 12-lead ECGs will be recorded at Screening, Check-in (Day -1), Day 1 (predose [within 0.5 hours before dosing the SC injection]), and Final Visit Day 127/ET. When an ECG recording is scheduled for the same day as blood draws (eg, PK or AVA sampling), the ECG recording will be collected 5 minutes before the nominal time of the blood sample.
(j) With the exception of the Screening Visit, clinical laboratory tests (hematology, serum chemistry, and urinalysis) require a minimum 10-hour overnight fast.
(k) A serum pregnancy test is required for women of childbearing potential only. Pregnancy avoidance counseling will also be performed.
(l) An FSH level will be obtained on women who are postmenopausal (ie, 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).
(m) Subjects will be confined to the clinic for 2 nights (Day -1 to Day 2, inclusive). The total confinement period will be 2 days. Subjects are required to be considered clinically stable by the investigator or designee before discharge on Day 2. Subjects will return to the study units periodically according to the schedule for PK sampling and safety assessments.
(n) The pain scale will be administered immediately following the SC injection, and a second assessment will be performed between 15 and 30 minutes following the injection.
(o) Blood samples for determination of AVA will be collected at predose on Day 1 (within 0.5 hours before dosing), Days 29, 64, 85, 106, and 127/ET postdose. AVA positive samples will be further analyzed for neutralizing AVA. If a subject experiences an SAE, a blood sample for AVA assessment should be obtained at the unscheduled visit.
(p) Blood samples for PK analyses of vedolizumab will be collected beginning predose on Day 1 (within 0.5 hours before the SC injection) and then at 2, 8, 24, 72, 120, and 168 hours after Day 1 dosing, and on Days 10, 15, 29, 43, 64, 85, 106, and Final Visit Day 127/ET. If a subject experiences an SAE, a blood sample for PK analysis should also be obtained at the unscheduled visit. PK samples will be collected at ET at the discretion of the investigator.
(q) PTEs will be captured following the signing of the informed consent at Screening. Routine collection of AEs will occur from the administration of study drug until Final Visit Day 127/ET and the unscheduled visit. Any new AEs will be recorded in the CRFs and site source document. If any SAE is reported spontaneously to the investigator following the AE collection period, the event will be reported to the sponsor if it is considered to be 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 responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform study related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study related duties and functions, and should implement procedures to ensure the integrity of the study related duties and functions performed and any data generated.
4. Ensure that study related procedures; including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, 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 or the subject's

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

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

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening and throughout the duration of the study, and for and for 18 weeks after last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 18 weeks after last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

Appendix E Collection, Storage, and Shipment of Bioanalytical Samples

Instructions for Processing of Serum Samples for PK Analysis of Vedolizumab

1. Collect 5 mL of venous blood into a Becton-Dickinson Vacutainer. For all vedolizumab samples, blood samples should be collected into red stopper vacutainers. Direct venipuncture is the only 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 at room temperature in a 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 (VedolizumabSC-1022), matrix (ie, serum), analyte (vedolizumab), randomization sequence 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. 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 Quest Pharmaceutical Services (QPS), Newark, DE before shipment to QPS. "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.

A Phase 1, Open-Label, Randomized, Parallel Group Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Autoinjector in Healthy Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	15-Dec-2017 12:11 UTC
	Statistical Approval	15-Dec-2017 15:59 UTC
	Clinical Science Approval	17-Dec-2017 17:29 UTC
	Clinical Approval	18-Dec-2017 16:31 UTC

Protocol Clarification Letter
Takeda Pharmaceuticals Protocol No.: VedolizumabSC-1022
Date of Final Protocol: 11-Dec-2017
Date of Letter: 14-Feb-2018

A Phase 1, Open-Label, Randomized, Parallel Group Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Autoinjector in Healthy Subjects

This letter is generated to clarify the following discrepancies within the protocol.

1. Section 7.2 Exclusion Criteria #19 states the following: The subject has received any live vaccinations **within 30 days before Screening**. Whereas, Section 7.3 Excluded Medications, Supplements, Dietary Products Table 7.a states the following: All live vaccines, except for inactivated influenza vaccine are **prohibited 28 days prior to Check-in** (Day -1).

   Section 7.2 Exclusion Criteria #19 is the correct restriction to be followed regarding live vaccinations.

2. Section 9.5.1 Vital Sign Procedure states the following: Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Check-in (Day -1), Day 1 (pre-dose, post-dose), Days 8, 106±3, and Final Visit Day 127±3/Early Termination. Whereas, Appendix A Schedule of Study Procedures states the following: Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Check-in (Day -1), Day 1 (pre-dose, post-dose), and Final Visit Day 127±3/ET.

   Section 9.5.1 is correct regarding Vital Signs being obtained on Day 8 and Day 106±3.

The final protocol, dated 11-Dec-2017, was not amended to clarify these items; however, should a protocol amendment be needed in the future, these clarifications will be addressed.

PPD

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Protocol Clarification Letter for PPD Study No.: CA23621
SPONSOR Study No.: VedolizumabSC-1022
Date of Final Protocol: 11-Dec-2017
Date of Protocol Clarification Letter: 25-Apr-2018

A Phase 1, Open-Label, Randomized, Parallel Group Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Autoinjector in Healthy Subjects

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This protocol clarification letter (PCL) is generated to confirm the sample size to be enrolled in this definitive study based on recent data from the pilot study (VedolizumabSC-1021), and earlier studies performed by Takeda.

Based on the above-mentioned studies, a new sample size of 102 subjects per group for a total of 204 subjects was computed. This revised sample size was based on the assumption of a true ratio of approximately (~) 119% and an intersubject CV% of ~20% to meet the bioequivalence criteria of 80.00 - 125.00% with an expected power of ~ 51.7%. An ~ 8.8% drop-out rate was assumed for the sample size calculation.

As of the date of this PCL, 51 subjects per group have been dosed. Therefore, an additional 51 subjects per group will be enrolled and dosed.

The final protocol dated 11-Dec-2017 was not amended, therefore, this PCL is being written.

PPD

PPD

CCI [redacted]

Protocol Clarification Letter for CCI [redacted] Study No.: CA23621
SPONSOR Study No.: VedolizumabSC-1022
Date of Final Protocol: 11-Dec-2017
Date of Protocol Clarification Letter: 24-May-2018

A Phase 1, Open-Label, Randomized, Parallel Group Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Autoinjector in Healthy Subjects

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This protocol clarification letter (PCL) is generated to indicate that an additional clinical site will be added.

As per the Study Summary section of the protocol, it is estimated that 1 site in the United-States will be used for this clinical study. However, due to the increase in sample size, an additional clinical site in the United-states will be added for the study conduct. The Principal Investigator (PI), PPD will remain the responsible PI for the overall study.

The final protocol dated 11-Dec-2017 was not amended, therefore, this PCL is being written.

PPD [redacted]

PPD [redacted]