Title: An Open-Label, Multicenter and Open Enrollment Model, Postmarketing, Milk-Only Lactation Study to Assess Concentration of Vedolizumab in Breast Milk of Lactating Women With Active Ulcerative Colitis or Crohn's Disease Who Are Receiving Vedolizumab Therapeutically

NCT Number: NCT02559713

Protocol Approve Date: 25 July 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.

PROTOCOL AMENDMENT

An Open-Label, Multicenter and Open Enrollment Model, Postmarketing, Milk-Only Lactation Study to Assess Concentration of Vedolizumab in Breast Milk of Lactating Women With Active Ulcerative Colitis or Crohn's Disease Who Are Receiving Vedolizumab Therapeutically

Phase 4, Postmarketing Vedolizumab-4001 Milk-Only Lactation Study

Sponsor: Takeda Development Center Americas, Inc.
One Takeda Parkway
Deerfield, IL 60015
USA

Study Number: Vedolizumab-4001

IND Number: 009125 **EudraCT Number:** N/A

Compound: Vedolizumab for injection, for intravenous use

Date: 25 July 2017 **Amendment Number:** 02

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
25 March 2015	Initial Protocol	Not applicable	TDC Americas
06 April 2016	01	Substantial	TDC Americas
25 July 2017	02	Substantial	TDC Americas

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

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

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

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

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

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, 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 Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Protocol Amendment 02 Summary of Changes

Rationale for Amendment 02

This document describes the changes in reference to the protocol incorporating Amendment No. 02. The primary reason for this amendment is to remove an exclusion criterion and to remove enhanced screening and monitoring procedures.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only. For specific descriptions of text changes and where the changes are located, see Appendix F.

Changes in Amendment 02

1. Updated the Takeda responsible medical officer.
2. Changed the minimum number of sites and allowed for sites outside of the United States.
3. Updated background information.
4. Updated inclusion Criterion 5.
5. Updated inclusion Criterion 7.
6. Removed exclusion Criterion 3.
7. Removed exclusion Criterion 4.
8. Removed the electrocardiogram (ECG) procedure.
9. Removed all clinical laboratory tests (hematology, serum chemistry, urine drug screen, and urinalysis), except for the urine pregnancy test (human chorionic gonadotropin [hCG]) for women of childbearing potential.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** Vedolizumab for injection, for intravenous use	
Title of Protocol: An Open-Label, Multicenter and Open Enrollment Model, Postmarketing, Milk-Only Lactation Study to Assess Concentration of Vedolizumab in Breast Milk of Lactating Women With Active Ulcerative Colitis or Crohn's Disease Who are Receiving Vedolizumab Therapeutically	**IND No.: 009125**	**EudraCT No.: N/A**
Study Number: Vedolizumab-4001	**Phase:** 4	

Study Design:

This is an open-label, multicenter and open enrollment model, milk-only postmarketing study to assess concentrations of vedolizumab in breast milk of lactating women with active ulcerative colitis (UC) or Crohn's disease (CD) who are receiving vedolizumab therapeutically. Up to 12 (minimum of 10) lactating women with active UC or CD at least 18 years old will be enrolled in this study. This is a milk-only lactation study with maternal milk sampling throughout the dosing interval, which allows detection of the presence of vedolizumab in milk of lactating women. No samples will be collected from the breast-fed infants in this study. Mothers must be exclusively breast-feeding their infants (or not providing more than 1 supplemental bottle of formula/day) when enrolled in this study.

Treatment Group	No. of Subjects	Treatment
1	Up to 12 (minimum of 10) lactating women with active UC or CD	300 mg intravenous (IV) Infusion over 30 min

At the approximately scheduled dosing time based on an established vedolizumab maintenance regimen, subjects will report to the clinic, study site, or other healthcare provider (HCP) office at Check-in (Day 1) and receive a 30-minute IV infusion. Subjects will remain at the clinic, study site, or other HCP office until after the Day 1 pharmacokinetic (PK) and safety assessments are completed. It is anticipated that visits on Days 4, 8, 15, or 29 may be completed in the subject's home setting in the presence of a qualified nurse. To facilitate these visits, the subject should have access to a telephone. In most cases, home nurses performing a visit to a subject may complete study data forms that can be entered into the database by the contract research organization or site staff. In other cases, subjects may visit a clinic, study site, or other HCP office for assessments or to provide milk samples. The Study Exit/Follow-up safety assessment will occur on Day 57. The total duration on study for each subject will be approximately 3 months, including screening.

A schematic of the study design is presented below:

Screening	Check in	Dosing and PK/Safety Assessment	PK and Safety Assessment (a)	Study Exit/ Follow-up Visit (b)
Day -28 to -1	Day 1	Day 1	Days 2-57	Day 57 (±3)

(a) PK collections will occur on Days 4(±1), 8 (±2), 15 (±3), and 29 (±3).
(b) If abnormal, clinically significant findings are observed upon discharge, subjects may be brought back to the clinic for re-evaluation per investigator's discretion. The Study Exit/Follow-up visit should occur prior to subject receiving the subsequent, scheduled vedolizumab maintenance dose (not part of this study).

Primary Objective:

To assess the concentration of vedolizumab in breast milk of lactating women with active UC or CD who are receiving vedolizumab therapeutically.

Subject Population:

Lactating women with active UC or CD who are receiving vedolizumab therapeutically.

Number of Subjects: Up to 12 (minimum of 10) lactating women with active UC or CD	**Number of Sites:** Approximately 7 to 10 sites
Dose Level(s): 300 mg vedolizumab IV (commercial drug)	**Route of Administration:** IV infusion over 30 minutes
Duration of Treatment: 4 to 8 weeks (subject is on established vedolizumab maintenance therapy and received at least 1 dose of 300 mg of vedolizumab IV postpartum or has completed vedolizumab induction therapy [300 mg of vedolizumab IV at Week 0, Week 2, and Week 6])	**Period of Evaluation:** The total duration on study for each subject will be approximately 3 months, including Screening

Main Criteria for Inclusion:

Subject is on established vedolizumab maintenance therapy and received at least 1 dose of 300 mg of vedolizumab IV postpartum or has completed vedolizumab induction therapy (300 mg of vedolizumab IV at Week 0, Week 2, and Week 6), which has been commenced by the subject's treating physician for the treatment of active UC or CD prior to enrolling in this study. The subject has delivered a single, normal term infant (at least 37 weeks' gestation) and lactation is well established in the subject. Mothers must be exclusively breast-feeding their infant (or not providing more than 1 supplemental bottle of formula/day) when enrolled in the study.

A complete list of inclusion criteria is provided in Section 7.1.

Main Criteria for Exclusion:

The subject has history of breast implants, breast augmentation, or breast reduction surgery.

A complete list of exclusion criteria is provided in Section 7.2.

In addition, subjects may not use any excluded medications, supplements, or food products outlined in the protocol. Standard concomitant medications to be excluded are listed in Table 7.a.

Main Criteria for Evaluation and Analyses:

Pharmacokinetics:

Milk from each breast will be completely emptied using an electric milk pump at the specified time points (see table below) for the determination of vedolizumab concentrations in the milk. Milk collected from each breast at each time point will be pooled, and the total volume of milk collected and the starting and finishing time of each collection will be recorded. Two 5-mL aliquots of milk will be stored at -70°C until analysis of vedolizumab concentration by enzyme-linked immunosorbent assay (ELISA). Subjects with mastitis should not have milk samples collected until the infection is completely resolved. For milk sample collection on Days 4 through 57 (Days 4 through 29 for once every 4 weeks [Q4W] vedolizumab therapy), sites are encouraged to schedule the visit at approximately the same time as the Day 1 postdose sampling time to reduce the effect of diurnal variation.

Sample Type	Dosing Day	Time Postdose (hours)
Milk	1	Predose (60 minutes before the start of infusion) and approximately 1 hour after the end of infusion on Day 1, Days 4 (±1), 8 (±2), 15 (±3), 29 (±3), and Study Exit/Follow-up Visit (Day 57 [±3] (prior to the next scheduled dose for subjects on once every 8 weeks (Q8W) vedolizumab therapy)

Safety:

Safety parameters will include adverse events (AEs), physical examination findings, and vital signs. AEs will be recorded following administration of the vedolizumab and throughout the entire study thereafter. Vital signs will be recorded at Screening, Day 1 (predose, and at least 1 hour after the end of infusion), Days 4 (±1), 8 (±2), 15 (±3), 29 (±3), and Study Exit/Follow-up (Day 57 [±3]) or Early Termination. Vital signs will include oral body temperature measurement, blood pressure, respiration rate and pulse (beats per minute), measured after 5 minutes supine.

A complete list of safety assessments is provided in Section 9.1.

Laboratory Tests:

A urine pregnancy test will be performed during screening, Day 1and Study Exit/Follow-up Visit.

Statistical Considerations:
Pharmacokinetic Measures:

Concentrations of vedolizumab in milk will be summarized by scheduled time points using descriptive statistics. Individual milk concentration versus time data will be presented in a data listing. Milk PK parameters of vedolizumab, estimated daily infant dosage and percentage of maternal vedolizumab dose in breast milk will be summarized using descriptive statistics. Additional statistical analysis may be conducted, as appropriate.

Safety:

The number and percentage of subjects with treatment-emergent AEs (defined as any AEs, regardless of relationship to vedolizumab), AEs of special interest, and serious adverse events (SAEs), which occur on or after dosing in subjects, will be summarized by Medical Dictionary for Regulatory Activities system organ class, and preferred term overall, by severity, and by relationship to vedolizumab. Separate summaries will also be generated for treatment-related AEs overall and by severity. Baseline, postbaseline, and change from Baseline in vital signs will be summarized. Subjects with markedly abnormal values vital signs will be tabulated.

Sample Size Justification:

The sample size of 12 (minimum of 10) subjects is considered to be sufficient for this milk-only lactation study in women with active UC or CD who are being treated with vedolizumab. The sample size was not based on statistical power considerations.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

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

3.2 Principal Investigator/Coordinating Investigator

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

3.3 List of Abbreviations

5-ASA	5-aminosalicylic acid
AE	adverse event
allo-HSCT	allogenic hematopoietic stem cell transplantation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_t	area under the milk concentration-time curve from time 0 to time t
AUC_τ	area under the milk concentration-time curve during a dosing interval
CD	Crohn's disease
CFR	Code of Federal Regulations
C_{max}	maximum observed milk concentration
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal(ly)
GGT	γ-glutamyl transferase
hCG	human chorionic gonadotropin
HCP	healthcare provider
IAC	Independent Adjudication Committee
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IV	intravenous(ly)
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	nonsteroidal anti-inflammatory drug
PI	principal investigator
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PT	preferred term
PTE	pretreatment event
Q4W	once every 4 weeks
Q8W	once every 8 weeks
CCI	[redacted]
RAMP	Risk Assessment and Minimization for PML

RCC	Research Coordination Center
SAE	serious adverse event
SADR	serious adverse drug reaction
SAP	statistical analysis plan
SOC	system organ class
$t_{1/2z}$	terminal disposition half-life
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
TNF-α	tumor necrosis factor-alpha
UC	ulcerative colitis
ULN	upper limit of normal

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

Vedolizumab (also referred to as MLN0002 or Entyvio) is a humanized immunoglobulin G1 monoclonal antibody (mAb) directed against the human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$integrin mediates lymphocyte trafficking to the gastrointestinal (GI) mucosa and gut-associated lymphoid tissue through adhesive interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa [1-4]. Vedolizumab binds the $\alpha_4\beta_7$ integrin, antagonizing its adherence to MAdCAM-1 and as such, impairs the migration of gut homing leukocytes into GI mucosa. Thus, vedolizumab acts as a gut-selective immunomodulator.

The effectiveness and safety of vedolizumab intended for intravenous (IV) use (vedolizumab IV, vedolizumab for injection, for intravenous use) for ulcerative colitis (UC) and Crohn's disease (CD) have been established in pivotal phase 3 clinical studies in subjects who had not responded adequately to corticosteroids, immunomodulators, or tumor necrosis factor-alpha (TNF-α) antagonists. As of 19 November 2016, a total of 8 phase 1 studies in healthy subjects, 8 phase 1b/phase 2 studies in subjects with UC or CD, and 3 phase 3 studies in subjects with UC or CD have been completed. Fourteen clinical studies are currently ongoing in the vedolizumab development program.

As of 19 November 2016, approximately 4200 subjects (309 healthy subjects, 1811 subjects with UC, 2138 subjects with CD, 3 subjects undergoing allogenic hematopoietic stem cell transplantation (allo-HSCT), 1 subject with pouchitis, and 2 subjects with melanoma) have received at least 1 dose of vedolizumab across completed and ongoing company-sponsored interventional clinical studies. Vedolizumab exposure in interventional clinical studies 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. Approximately 450 subjects with UC or CD have received at least 1 dose of vedolizumab across ongoing company-sponsored noninterventional clinical studies. Based on drug shipment data as of 19 November 2016, the cumulative postmarketing patient exposure to vedolizumab IV globally is estimated to be approximately 77,382 patient-years.

Vedolizumab exhibits target-mediated drug disposition as characterized by linear and nonlinear processes of elimination after single-dose administration. Following IV dosing, vedolizumab concentrations fell in a biexponential fashion until concentrations reached approximately 1 to 10 µg/mL with a serum terminal elimination half-life ($t_{1/2z}$) of approximately 25 days. Thereafter, vedolizumab concentrations fell in a nonlinear fashion.

Similar pharmacokinetics (PK) was observed in healthy subjects and in subjects with UC or CD. Results from population PK analyses suggest that while body weight and serum albumin are predictors of clearance, their effects are not considered clinically relevant. The PK of vedolizumab was similar in Japanese and Western subjects with UC. Vedolizumab PK was not affected by the coadministration of other immunosuppressive agents, including 6-mercaptopurine,

aminosalicylates, methotrexate, or azathioprine. As a mAb, the potential of vedolizumab to directly affect or be affected by cytochrome P-450 enzymes or transporters has not been tested.

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

4.2 Rationale for the Proposed Study

UC and CD are chronic, idiopathic, inflammatory conditions of the GI tract that peak in incidence during the reproductive years [5]. Therefore, the safety of medications to treat UC and CD during pregnancy and lactation is of significant interest to women patients of childbearing potential, as these medications may be transferred in utero or through breast milk from nursing inflammatory bowel disease (IBD) patients to their newborns [5]. Based on literature, mAbs, including selected TNF-α antagonists, are excreted in human milk; however, these antibodies in breast milk do not enter the neonatal and infant circulation in substantial amounts [6-10]. Low levels CCI of vedolizumab were detected on postpartum CCI in the milk CCI treated with CCI of vedolizumab (CCI) dosed every CCI weeks; however, vedolizumab was not detected in the milk of any monkeys (n=7) treated with CCI It is unknown whether vedolizumab is present in human milk.

The purpose of this postmarketing clinical study is to assess concentrations of vedolizumab in breast milk of lactating women with active UC or CD who have been on established vedolizumab IV maintenance treatment during the study period. This study is intended to fulfill the sponsor's postmarketing commitment to conduct a milk-only lactation study as specified in the vedolizumab approvable letter from the Food and Drug Administration (FDA).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To assess the concentration of vedolizumab in breast milk of lactating women with active UC or CD who are receiving vedolizumab IV therapeutically.

5.2 Endpoints

5.2.1 Primary Endpoint

- Concentration of vedolizumab in breast milk at predose and 1 hour after the end of infusion on Day 1, and on Days 4, 8, 15, 29, and 57 (for subjects on Q8W vedolizumab therapy only).

5.2.2 Other Endpoints

- Area under the milk concentration-time curve from time 0 to time t (AUC_t), area under the milk concentration-time curve during a dosing interval (AUC_τ), maximum observed milk concentration (C_{max}) and time of first occurrence of C_{max} (t_{max}), for vedolizumab.
- Estimated daily infant dosage on each sampling day and over the dosing interval.
- Percentage of maternal dosage consumed in breast milk by infants at each sampling day and over the dosing interval.

5.2.3 Safety Endpoints for Lactating Women

- Treatment-emergent adverse events (TEAEs).
- Vital sign measurements (blood pressure, heart rate, and oral temperature).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is an open-label, multicenter and open enrollment model, postmarketing milk-only study to assess concentrations of vedolizumab in breast milk of lactating women with active UC or CD who are receiving vedolizumab therapeutically. Up to 12 (minimum of 10) lactating women with active UC or CD who are at least 18 years old will be enrolled in this study. This study combines a traditional site-based approach and an open enrollment model to maximize enrollment and maintain efficiency and to meet local regulations. Where approved by the institutional review board (IRB), the open enrollment model may be implemented in addition to the traditional site-based approach.

Principal investigators (PIs) may be given the option to enroll and manage only subjects treated at their site (ie, traditional site) and/or to serve as a central PI (ie, provide oversight of subjects enrolled through the open enrollment model). The PIs are appropriately trained physicians who are responsible for providing oversight of the study, ensuring protocol adherence, and assessing safety of subjects and their infants enrolled in the study. Traditional sites are responsible for identifying eligible subjects from their institution, consenting/enrolling subjects, performing study procedures, coordinating home healthcare visits, assessing subjects' safety, and collecting and entering data into the electronic case report form (eCRF).

In addition to the traditional site-based approach, having an open enrollment approach provides the opportunity for other eligible subjects to self-enroll if they reside outside of the geographic location of the traditional sites. Enrollment is facilitated by CCI Research Coordination Center (RCC) in the US. The RCC staff (who are formally trained in the appropriate methods for handling study procedures) coordinate enrollment and facilitate study management between:

- A subject enrolled using the open enrollment service.
- The subject's designated central site/investigator.
- The subject's healthcare providers (HCPs).
- The subject's home healthcare nurses.

In the open enrollment model, eligible subjects are identified through awareness activities directed at the subject and her HCPs. The subject contacts CCI RCC for information about the study and, if interested in proceeding, answers prescreening questions. Interested eligible subjects provide written informed consent and medical release. The RCC assigns the subject to a central site/PI. The central PI, with the assistance of the RCC, will work with the subject and her HCP to assess eligibility. Screening activities are coordinated by the RCC through the subject's local HCP, and the findings are shared with the central PI. The central PI will be responsible for directing the activities of the homecare nurse and will ensure that all adverse events (AEs) are properly assessed and reported and will provide oversight for the study. The central PI may also be serving as a traditional site PI.

Upon confirmation of eligibility at initial screening by the central PI, the RCC facilitates delivery of study-related materials (ie, electronic breast pump) to the subject. The RCC facilitates home visits with the designated local home healthcare agency. A breast pump and supplies for collecting the milk samples will be provided to the subject. Additional data collection and AE reporting in accordance with collection and reporting procedures described in Section 10.2 are facilitated by the RCC. The RCC provides ongoing assistance to the central site/investigator throughout the study.

This is a milk-only lactation study with maternal milk sampling throughout the dosing interval, which allows detection of the presence of vedolizumab in milk of lactating women. No samples will be collected from the breast-fed infants in this study. Mothers must be exclusively breast-feeding their infants (or not providing more than 1 supplemental bottle of formula/day) when enrolled in this study.

Subjects with an established vedolizumab maintenance regimen and have received at least 1 dose of 300 mg of vedolizumab IV postpartum or have completed vedolizumab induction therapy (300 mg of vedolizumab IV at Week 0, Week 2, and Week 6) will report to the clinic, study site, or other HCP office at Check-in (Day 1) and receive a 30-minute IV infusion of 300 mg vedolizumab at their approximately scheduled dosing time. Subjects will remain at the clinic, study site, or other HCP office until after the Day 1 PK and safety assessments are completed. It is anticipated that visits on Days 4 (±1), 8 (±2), 15 (±3), or 29 (±3) may be completed in the subject's home setting in the presence of a qualified nurse. To facilitate these visits, the subject should have access to a telephone. In most cases, home nurses performing a visit to a subject may complete study data forms that can be entered into the database by the RCC or site staff. In other cases, subjects may visit a clinic, study site, or other HCP office for assessments or to provide milk samples. The Study Exit/Follow-up safety assessment will occur on Day 57 (±3). The total duration on study for each subject will be approximately 3 months, including Screening.

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

Table 6.a Summary of Treatment Group

Treatment Group	No. of Subjects	Treatment
1	Up to 12 (minimum of 10) lactating women with active UC of CD	300 mg IV Infusion over 30 minutes

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

Pretreatment Period		Treatment Period		
Screening	**Check-in**	**Dosing and PK/Safety Assessment**	**PK and Safety Assessment (a)**	**Study Exit/Follow-up Visit (b)**
Days -28 to -1	Day 1	Day 1	Days 2-57	Day 57 (±3)

(a) PK collections will occur on Days 4 (±1), 8 (±2), 15 (±3), 29 (±3), and 57 (±3) (for subjects on Q8W therapy).
(b) If abnormal, clinically significant findings are observed upon Study Exit/Follow-up, subjects may be brought back to the clinic, study site, or other HCP office for re-evaluation per investigator's discretion. The Study Exit/Follow-up visit (Day 57 [±3]) should occur prior to subject receiving the subsequent, scheduled vedolizumab maintenance dose (not part of this study).

6.2 Justification for Study Design, Dose, and Endpoints

This study will assess concentrations of vedolizumab in breast milk of lactating women with active UC or CD who have been on established vedolizumab maintenance treatment and received at least 1 dose of 300 mg of vedolizumab IV postpartum or have completed vedolizumab induction therapy (300 mg of vedolizumab IV at Week 0, Week 2, and Week 6) before enrolling in this study. The dose selected in this study is the label recommended dose for treatment of patients with actively moderately or severely active UC or CD. Serial milk samples will be collected over the dosing interval (4 to 8 weeks) following the vedolizumab treatment to determine the PK parameters of vedolizumab in breast milk and to estimate the infant dosage on each sampling day, mean daily infant dosage over the dosing interval through breast milk, and percentage of maternal dose consumed in breast milk by the infants. During each sample collection time point, milk will be completely expressed from each breast and pooled before sampling to ensure the observed drug concentration in milk mimics the mean drug level during each feeding. The results of this study may be used to appropriately inform the Nursing Mother's subsection of the labeling.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the compound, such that the risk/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 Investigational Sites

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

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

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

7.1 Inclusion Criteria

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

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is female and at least 18 years of age at the time of informed consent.
4. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent and throughout the duration of the study.

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

5. The subject is on established vedolizumab maintenance therapy and received at least 1 dose of 300 mg of vedolizumab IV postpartum or has completed vedolizumab induction therapy (300 mg of vedolizumab IV at Week 0, Week 2, and Week 6), which has been commenced by the subject's treating physician for the treatment of active UC or CD prior to enrolling in this study.
6. The subject has delivered a single, normal term infant (at least 37 weeks' gestation); a mother-infant pair is required.
7. The subject is at least 5 weeks postpartum by Day 1.
8. Lactation is well established and the mother is exclusively breast-feeding her infant (or not providing more than 1 supplemental bottle of formula/day) when enrolled in the study.
9. The decision to treat with vedolizumab or to breast-feed is made independently from and prior to the subject consenting to participate in this study.
10. The subject plans to continue breast-feeding at least throughout the duration of this study.
11. The subject agrees to use only the emollient or nipple cream recommended by the investigator for use during the Sampling Period.

7.2 Exclusion Criteria

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

1. The subject has received any investigational compound or approved biologic or biosimilar agent, except for vedolizumab within 60 days prior to enrollment in the study.
2. Within 30 days prior to enrollment, the subject has received any of the following for the treatment of underlying disease:
   a) Nonbiologic therapies (eg, cyclosporine) other than those specifically listed in protocol Section 7.4, *Permitted Medications for the Treatment of UC or CD*).
   b) An approved nonbiologic therapy in an investigational protocol.
3. The subject has received any live vaccinations within 30 days prior to vedolizumab administration.
4. The subject has clinically significant infection (eg, pneumonia, pyelonephritis) or chronic infection within 30 days prior to enrollment.
5. The subject is an immediate family member, study site employee, or is in a dependant 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.
6. The subject has evidence of unstable or uncontrolled, clinically significant cardiovascular, central nervous system, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic or other medical disorder, including serious allergy, asthma, hypoxemia, hypertension, seizures or allergic skin rash that, in the opinion of the investigator, would confound the study results or compromise subject safety. Additionally, if there is any finding in the subject's medical history or physical examination giving reasonable suspicion of a disease that would contraindicate taking vedolizumab, or a similar drug that might interfere with the conduct of the study.
7. The subject has had any surgical procedure requiring general anesthesia within 30 days prior to enrollment or is planning to undergo major surgery during the study period.
8. The subject has any history of malignancy, except for the following: (a) adequately treated nonmetastatic basal cell skin cancer; (b) squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to enrollment; and (c) history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years prior to enrollment. Subjects with remote history of malignancy (eg, >10 years since completion of curative therapy without recurrence) will be considered based on the nature of the malignancy and the therapy received and must be discussed with the sponsor on a case-by-case basis prior to enrollment.
9. The subject has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease.

10. The subject has a positive progressive multifocal leukoencephalopathy (PML) subjective symptom checklist at screening.
11. The subject has a current or recent history (within 1 year prior to enrollment) of alcohol dependence or illicit drug use.
12. The subject has active psychiatric problems that, in the investigator's opinion, may interfere with compliance with the study procedures.
13. The subject is unable to participate in all the study visits or comply with study procedures.
14. The subject has history of breast implants, breast augmentation, or breast reduction surgery.
15. The subject has a prior history of difficulty establishing lactation.
16. The subject has taken any excluded medication, supplements, or food products during the time periods listed in the Excluded Medications and Dietary Products table listed in Section 7.3.
17. The subject has donated or lost 450 mL or more of her blood volume (including plasmapheresis), or had a transfusion of any blood product within 45 days prior to Day 1.

7.3 Excluded Medications, Dietary Products, Procedures, and Treatments

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until the Study Exit/Follow-up visit.

Table 7.a Prohibited Medications

60 days prior to Check-in (Day 1)	30 days prior to Check-in (Day 1)
Investigational or approved biologic or biosimilar agent, except vedolizumab.	Prescription medications (including oral estrogen contraceptives) which may interfere with milk assays (a)
	OTC medications and supplements (b)
	All live vaccines.

OTC=over-the-counter.
(a) Nonbiologic therapies specifically listed in protocol Section 7.4, Permitted Medications for the Treatment of UC or CD are permitted.
(b) Occasional use of acetaminophen (≤1 g/day) or other medication as approved by Takeda on a case-by-case basis is allowed. Stable doses of multivitamins will be allowed.

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

7.4 Permitted Medications for the Treatment of UC or CD

7.4.1 Permitted Medications for the Treatment of UC

- Oral or topical (rectal) 5-aminosalicylic acid (5-ASA) compounds.

- Oral corticosteroid therapy (prednisone at a stable dose ≤30 mg/day, or equivalent steroid).
- Topical (rectal) corticosteroid enemas/suppositories.
- Azathioprine or 6-mercaptopurine.
- Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea.
- Probiotics (eg, *Lactobacillus*, *S. boulardii*).
- Antibiotics used for the treatment of IBD (ie, ciprofloxacin) not contraindicated in breast-feeding.

7.4.2 Permitted Medications for the Treatment of CD

- Oral or topical (rectal) 5-ASA compounds.
- Oral corticosteroid therapy (prednisone at a stable dose ≤30 mg/day, budesonide at a dose ≤9 mg/day, or equivalent steroid).
- Topical (rectal) corticosteroid enemas/suppositories.
- Antibiotics used for the treatment of IBD (ie, ciprofloxacin) not contraindicated in breast-feeding.
- Azathioprine or 6-mercaptopurine.
- Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea.
- Probiotics (eg, *Lactobacillus*, *S. boulardii*).

7.5 Excluded Medications

- Medications for UC and CD other than those listed in Section 7.4.
- All live vaccines, during study treatment and for at least 6 months after the last dose of vedolizumab.
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use (note: occasional use of NSAIDs and acetaminophen and daily use of baby or low-dose [81-162.5 mg] aspirin for cardiovascular prophylaxis are permitted).

7.6 Diet, Fluid, Activity Control

There are no restrictions.

7.7 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.14.

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.
2. Significant protocol deviation. The discovery after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE.
5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

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

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

7.8 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 7.7. In addition, a subject may discontinue 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. Subjects discontinued or withdrawn from the study prior to Day 15 may be replaced if the sponsor decides it is necessary.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Study Medication

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Vedolizumab For Injection, For Intravenous Use

The study sites will not be supplied with packaged medication from Takeda as subjects will stay on established vedolizumab (commercial drug).

8.1.2 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, study site, or other HCP office under the supervision of the PI or designees as indicated in Table 8.a.

Table 8.a Dose and Regimen

Treatment Group	No. of Subjects	Treatment
1	Up to 12 (minimum of 10) lactating women with active UC or CD	300 mg IV Infusion over 30 min.

8.1.3 Preparation, Reconstitution, and Dispensation

The investigational pharmacist or designee will prepare the study treatment under standard aseptic conditions. Refer to Entyvio package insert for detailed instructions. The expiry date and lot number of each medication must be recorded in study files.

8.1.4 Overdose

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

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

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

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

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will receive treatment according to study schedule.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

Investigator supplies commercial drug. The study sites will not be supplied with packaged medication from Takeda as subjects will stay on established vedolizumab (commercial drug).

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, site personnel, or other HCP whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

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

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed, including requesting that a subject fast for laboratory evaluations.

In the open enrollment model, CCI RCC will provide interested eligible subjects with the informed consent form (ICF) and medical release form. The central PI will contact the subject via phone to discuss the ICF and answer any questions the subject may have regarding the study. The RCC will send the subject a copy of the fully signed ICF once available.

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 or age, sex, Hispanic ethnicity, race as described by the subject, height, weight, alcohol use, reproductive status (including last menstrual period, lactation history, and failure to thrive of prior breast-fed infants) and smoking status of the subject at Screening.

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

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 60 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A physical examination will be performed at Screening, Day 1(baseline; defined as the assessment prior to first dose of vedolizumab), and Day 57/Early Termination/Follow-up (±3). For subjects participating through open enrollment, the physical examination may be performed by the subject's local HCP, and a record of that examination provided to the investigator as documentation. The physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system;

(10) lymph nodes; (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

Any abnormal change from the baseline physical examination (Day 1 predose) must be assessed as not clinically significant or clinically significant by the investigator and recorded in the source document and eCRF.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment must be assessed as not clinically significant or clinically significant by the investigator and recorded in the source document and eCRF. 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 eCRF described in Section 10.0.

9.1.4 Weight and Height

A subject should have weight and height measured at Screening (weight only at Day 1) measured while wearing indoor clothing and with shoes off.

9.1.5 Vital Sign Procedure

Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Day 1 (predose, and at least 1 hour after the end of the infusion), Days 4, 8, 15 and 29, and Study Exit/Follow-up (Day 57) or Early Termination and will be measured after 5 minutes supine.

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 milk collections, the milk collections will take priority.

9.1.6 Documentation of Concomitant Medications

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

9.1.7 Need for Rescue Medications

In this study, any new medication or any increase in dose of a baseline medication required to treat new or unresolved UC and CD symptoms (other than antidiarrheals for control of chronic diarrhea) is considered a rescue medication and must be recorded. Rescue medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise subject safety.

9.1.8 Documentation of Concurrent Medical Conditions

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

9.1.9 Procedures for Clinical Laboratory Samples

A urine pregnancy test (human chorionic gonadotropin [hCG]) will be performed at Screening, on Day 1 prior to dosing, and on Day 57 prior to the next scheduled dose.

9.1.10 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, (57 days after last dose of study medication), female subjects who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova or breast milk during this period.

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

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

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

Barrier methods (each time the subject has intercourse):	**Intrauterine devices (IUDs):**	**Hormonal contraceptives (only Non-estrogen containing products allowed:**
• Male condom PLUS spermicide. • Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide. • Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.	• Copper T PLUS condom or spermicide. • #Progesterone T PLUS condom or spermicide.	• Implants. • Hormone shot/injection. • Minipill.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they

understand the requirements for avoidance of pregnancy, donation of ova, during the course of the study.

During the course of the study, regular urine hCG pregnancy tests will be performed for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A). In addition to a negative urine hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test prior to receiving any dose of study medication. A urine hCG test will also occur at the Study Exit (Day 57)/Early Termination Visit.

9.1.11 Pregnancy

If any subject is found to be pregnant during the study, she will be withdrawn immediately and offered to enroll in the ongoing pregnancy registry.

All pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, should be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.12 PML Checklist

Clinic staff, or other HCP, will administer the subjective PML checklist at the Screening Visit, prior to dosing on Day 1, and at the Study Exit/Follow-up (Day 57) or Early Termination Visit. Subjects will be provided a PML wallet card at Screening and at Study Exit/Follow-up or the Early Termination visit.

9.1.13 PK Sample/Milk Collection

9.1.13.1 Collection of Breast Milk for PK Sampling

Milk from each breast will be completely emptied using an electric milk pump at the specified time points according to Table 9.a for the determination of vedolizumab concentrations in the milk. Milk collected from each breast at each time point will be pooled, and the total volume of milk collected and the starting and finishing time of each collection will be recorded on the source document and eCRF. Two 5-mL aliquots of milk will be stored at -70°C until analysis of vedolizumab concentration by enzyme-linked immunosorbent assay (ELISA). Subjects with mastitis should not have milk samples collected until the infection is completely resolved. If mastitis is not resolved within the allowed window for sample collection, the sample should be collected at an unscheduled visit as close to scheduled time point as possible. If the unscheduled collection overlaps with the next scheduled time point, the missed sample collection should be skipped. For milk sample collection on Days 4 through 57 (Days 4 through Day 29, prior to next scheduled dose, for subjects on once every 4 weeks [Q4W] vedolizumab therapy), sites are encouraged to schedule the visit at approximately the same time as the Day 1 postdose sampling time to reduce the effect of diurnal variation. It is anticipated that visits on Study Days 4 (±1), 8 (±2), 15 (±3), or 29 (±3) may be completed in the subject's home setting in the presence of a qualified nurse. To facilitate these visits for milk sample collection, the subject should have access

to a telephone. In most cases, nurses performing a visit to a subject may complete study data forms that can be obtained and entered into the database by the RCC or site staff. In other cases, subjects may visit a qualified clinic, study site, or other HCP office to provide milk samples. Instructions for sample processing and shipping are provided in Appendix E. Additional instructions for homecare nurses will be provided in a separate manual.

Table 9.a Collection of Milk Samples for PK Analysis

Sample Type	Dosing Day	Scheduled Time Postdose (hours)
Milk	1	Predose, (60 minutes before the start of infusion) and approximately 1 hour after the end of infusion on Day 1, Days 4 (±1), 8 (±2), 15 (±3), 29 (±3), and Study Exit (Day 57 [±3] for Q8W regimen only) (prior to next scheduled dose).

9.1.13.2 Bioanalytical Methods

Milk concentrations of vedolizumab will be measured by a validated ELISA to measure vedolizumab concentrations.

9.1.13.3 PK Parameters

Milk PK parameters of vedolizumab will be derived using non-compartmental analysis methods. The PK parameters of vedolizumab will be determined from the concentration-time data for all evaluable subjects. Actual mid-point sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of vedolizumab in milk: C_{max}, AUC_t, AUC_τ, and t_{max}. The estimated daily infant dosage through breast milk on each sampling day, the mean daily infant dosage over the dosing interval and the percentage of weight-adjusted maternal dose consumed in breast milk may be calculated using the corresponding breast milk concentration(s) on the sampling day or AUC_τ values and the standardized breast-fed infant milk consumption of 150 mL/kg/day per FDA guidance on clinical lactation studies [11], as appropriate. Additional PK parameters may be calculated.

Symbol/Term	Definition
AUC_t	Area under the milk concentration-time curve from time 0 to time t.
AUC_τ	Area under the milk concentration-time curve during a dosing interval (τ).
C_{max}	Maximum observed milk concentration.
t_{max}	Time of first occurrence of C_{max}.
Daily Infant Dosage	Estimate daily dosage consumed by the infant through breast milk; calculated as observed concentration in milk on a sampling day×150 mL/kg/day (daily dosage on the corresponding sampling day) or AUC_τ/τ×150 mL/kg/day (daily dosage over the dosing interval).
% Maternal Dosage	Percentage of the maternal dose consumed in breast milk over the dosing interval; calculated as Infant Daily Dosage×τ/Weight-adjusted Maternal Dosage×100.

9.1.14 Documentation of Screen Failure

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

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

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

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

9.1.15 Documentation of Study Entrance

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

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

9.2 Monitoring Subject Treatment Compliance

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

9.3 Schedule of Observations and Procedures

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

9.3.1 Screening

Subjects will be screened within 28 days prior to Check-in (Day 1). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.14 for procedures for documenting screening failures.

9.3.2 Study Entrance

Study entrance will take place on Check-in (Day 1).

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for study entrance, the subject will be administered their dose of study medication in the unit or other HCP office under the supervision of the investigator or designee, as described in Section 8.2. The procedure for documenting Screening failures is provided in Section 9.1.14.

9.3.3 Study Exit/Follow-up Visit

The Study Exit/Follow-up Visit will be performed 57 days (±3) after the dose of vedolizumab.

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

9.3.4 Early Termination

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

The PK milk sample collection should be collected at the Early Termination Visit, if possible. The site may seek guidance. For example, collect samples if early withdrawal is due to an AE.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

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

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs 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).

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 condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening

or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

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

Changes in severity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

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

10.1.4 SAEs

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

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

Table 10.a Takeda Medically Significant AE List

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

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

10.1.5 Special Interest AEs

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda. Refer to Section 10.2.1.4 for information for special interest AE reporting.

Special interest AEs for vedolizumab below should be reported to Takeda within 24 hours.

10.1.6 Severity of PTEs and AEs

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

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

10.1.7 Causality of AEs

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

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

10.1.8 Relationship to Study Procedures

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

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

10.1.9 Start Date

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

10.1.10 Stop Date

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

10.1.11 Frequency

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

10.1.12 Action Concerning Study Medication

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

10.1.13 Outcome

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

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

- Start of AE collection: AEs must be collected from start of study medication administration.

- End of AE collection: AEs must be collected for 57 Days following the last dose of vedolizumab.

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

Collection of AEs will commence from the time that the subject is first administered study medication (Day 1). Routine collection of AEs will continue until the Study Exit Visit (Day 57 ±3 days after their dose of vedolizumab).

10.2.1.2 PTE and AE Reporting

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

AEs relating to the infant that are spontaneously reported should be collected and entered into the specific AE eCRF.

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

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

10.2.1.3 AE Collection Involving Medically Anticipated Clinical Events

CD and UC are associated with certain characteristic signs and symptoms including diarrhea, rectal bleeding, and abdominal pain that may be present at baseline and persist or fluctuate based on the individual subject's disease history during the course of the study. These signs and symptoms will be collected as AEs.

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

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

10.2.1.4 Special Interest AE Reporting

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

Hypersensitivity Reactions

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

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

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

Serious Infection

Subjects will be monitored for signs and symptoms of infection and for lymphopenia during the study. Subjects with signs and symptoms suggestive of infections, including GI infections, will be

treated as clinically indicated. Interventions may include antibiotic treatment, if appropriate and/or discontinuation of concomitant immunomodulators. Blood, sputum, urine, and/or stool cultures should be obtained as appropriate for the detection and diagnosis of infection. Withholding or terminating vedolizumab administration may be considered as described in Section 10.1.12.

Malignancies

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

Other

Other special interest AEs include hepatotoxicity and PML, which are discussed in Sections 10.3 and 11.1.1, respectively.

10.2.2 Collection and Reporting of SAEs

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

A Takeda SAE eCRF or paper 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 medication(s).
- Causality assessment.

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

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

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

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 applicable unexpected serious adverse drug reactions (SADRs) to regulatory authorities, including the European Medicines Agency, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, unexpected SADRs will be submitted to the regulatory authorities as expedited report within 15 days, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the study. The investigator site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No data safety monitoring committee will be used in this study.

11.1 Adjudication Committee

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

11.1.1 Risk Assessment and Minimization for PML (RAMP Program)

To address the theoretical risk of the development of PML in subjects treated with vedolizumab, the sponsor, with input from renowned PML experts, has developed a Risk Assessment and Minimization for PML, the RAMP program. The complete description of the RAMP program, including materials and instructions for its implementation and monitoring, is included in the Study Manual. The RAMP program is focused on early clinical detection and management of that specific safety risk, including the discontinuation of vedolizumab, if applicable. Subjects are assessed for signs and symptoms of PML prior to administration of vedolizumab 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 subject evaluation and management as defined in the IAC charter.

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

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 CRFs (Electronic and Paper)

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

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

Data collected by the subject's HCP or homecare nurse will be recorded by the HCP or home nurse on the applicable study forms, home care worksheets, and source documents. The subject's HCP or home nurse will send the original, completed documents to CCI RCC or the investigator/site via courier. If the original, completed documents are sent to CCI RCC, the RCC will send the documents to the investigator/site via courier. Site staff or CCI RCC will transcribe the data directly onto the eCRFs.

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

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

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

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

13.1.1 Analysis Sets

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

The PK set will consist of all subjects who are enrolled and received 1 dose of vedolizumab and have at least 1 measurable milk concentration.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects by treatment group. 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, ethnicity, and race).

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

13.1.3 PK Analysis

Concentrations of vedolizumab in milk will be summarized by scheduled time points using descriptive statistics. Individual milk concentration versus time data will be presented in a data listing. Milk PK parameters of vedolizumab, estimated daily infant dosage and percentage of maternal vedolizumab dose in breast milk will be summarized using descriptive statistics. Additional statistical analysis may be conducted, as appropriate.

13.1.4 Safety Analysis

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA. A TEAE is defined as an AE with onset occurring within 57 days after vedolizumab administration. TEAEs will be listed and summarized. AEs with onset dates before the start of study medication or 57 days after last dose of study medication will be listed, but they will not be included in the summary table.

TEAEs will be summarized by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, adverse events of special interest (ie, serious infections, including opportunistic infects such as PML, malignancies, liver injury, infusion reactions), relationship of AEs to vedolizumab (related vs not-related), severity of AEs and related AEs. AEs leading to vedolizumab discontinuation and SAEs will be listed. Data listings will be provided for all AEs including PTE, TE AEs, AEs leading to vedolizumab discontinuation, and SAEs.

13.1.4.1 Clinical Laboratory Evaluation

Other than urine pregnancy tests at Screening and Days 1 and 57, no clinical laboratory assessments will be conducted during this study.

13.1.4.2 Vital Signs

Individual results of vital signs that meet Takeda's markedly abnormal criteria to be defined in the SAP will be listed and summarized. Baseline, postdose, and change from baseline in vital sign measurements will be summarized. All vital signs data will be provided in the data listings.

13.1.4.3 Other Variables

The physical examination findings will be presented in data listings.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

The sample size of 10 to 12 subjects is considered to be sufficient for this milk-only lactation study in women with active UC or CD who are being treated with vedolizumab IV. The sample size was not based on statistical power considerations.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or 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.

Protocol Deviation Forms are to be completed for PK samples collected outside of the following intervals:

Table 14.a Windows for PK Milk Sample Collection Start Time

Minutes/Days	Nominal Sampling Time
no more than 60 minutes predose	0 hour
±15 minutes	immediately postdose to ≤6 hours
±1 day	>6 hours to ≤4 days postdose
±2 days	>4 days to ≤8 days postdose
±3 days	>8 days postdose

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 institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

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

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

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

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

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

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

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing. For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor. Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

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Appendix A Schedule of Study Procedures

	Screening	Treatment					
Study Day:	**Days -28 to -1**	**Day 1**	**Day 4 ±1**	**Day 8 ±2**	**Day 15 ±3**	**Day 29 ±3**	**Day 57±3 Study Exit/ET/Follow-up (a)**
Informed consent (b)	X						
Inclusion/exclusion criteria	X	X					
Demographics and medical history	X						
Lactation history	X						
Medication history	X						
Physical examination (c)	X	X					X
PML subject wallet card	X						X
PML checklist (d)	X	X					X
Vital signs (e)	X	X	X	X	X	X	X
Weight and height (f)	X	X					X
Concomitant medications (g)	X	X	X	X	X	X	X
Urine pregnancy test (h)	X	X					X
Vedolizumab dosing		X					
PK milk collection (i)		X	X	X	X	X	X
PTE/AE assessment (j)	X	X	X	X	X	X	X

Footnotes are on the next page.

(a) Conduct procedures for subjects discontinued early per Protocol Section 7.8. The PK sample should be collected at the Early Termination Visit, if possible. Study Exit/Follow-up visit should occur prior to subject receiving the subsequent, scheduled vedolizumab maintenance dose (not part of this study).
(b) Informed consent must be signed before any study-specific procedures are performed.
(c) All physical examinations are to be performed by the PI or subinvestigator at Screening, Day 1 (predose), and Day 57 (±3)/Study Exit/Follow-up. Clinically significant findings on the physical examination that occur postdose of vedolizumab will be recorded as AEs. For subjects participating in open enrollment, the physical examination may be performed by the subject's local HCP, and a record of that examination provided to the investigator as documentation.
(d) The PML checklist will be administered at screening, prior to dosing on Day 1 and Study Exit/Early Termination (ET)/Follow-up on Day 57.
(e) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, on Day 1 (predose and at 1 hours after the end of infusion), Days 4, 8, 15, and 29, and Study Exit/Follow-up (Day 57) or Early Termination) will be measured after 5 minutes supine.
(f) Height will only be collected at Screening.
(g) Record all ongoing medications from Screening and throughout the study.
(h) Urine pregnancy test will be performed at Screening, on Day 1 prior to dosing and on Day 57 prior to the next scheduled dose.
(i) Milk samples for PK analyses will be collected at predose (within 60 minutes prior to the start of infusion) and approximately 1 hour after the end of infusion on Day 1, and on Days 4, 8, 15, 29, and 57 (for Q8W regimen only), prior to the next scheduled dose). Subjects with mastitis should not have milk samples collected until the infection is completely resolved. Subjects unable to return to the clinic for Days 4, 8, 15, or 29 may have their milk samples collected at home by a qualified and trained homecare nurse.
(j) PTEs will be captured immediately following the signing of the informed consent at Screening. The routine collection of AEs will be captured from first dose of study drug and will continue until Study Exit/Early Termination/Follow-up. Any spontaneously reported AEs/SAEs will continue to be reported until Study Exit/Early Termination/Follow-up.

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

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

Appendix C Elements of the Subject Informed Consent

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

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

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

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

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening and throughout the duration of the study, and for 57 days after last dose of study medication. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, she will be withdrawn immediately and offered to enroll in the pregnancy registry.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

Appendix E Collection, Storage, and Shipment of Bioanalytical Samples

Instructions for Processing of Milk Samples for PK Analysis of Vedolizumab

1. Milk from each breast will be completely emptied using an electric milk pump at the specified time points for the determination of vedolizumab concentrations in the milk. Milk collected from each breast at each time point will be pooled, and the total volume of milk collected and the starting and finishing time of each collection will be recorded on the source document and eCRF.
2. The pooled milk sample should be gently mixed and two aliquots of approximately 5.0 mL should be removed and placed into 2 appropriately labeled cryotubes.
3. Cryotube labeling may include protocol number (Vedolizumab-4001), sample matrix (ie, milk) subject ID, profile day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
4. Cap the labeled storage tubes and freeze the milk samples immediately at approximately -70°C or lower until shipment to CCI [redacted] On visit days when milk PK samples are collected by the subject's HCP, or at the subject's home by the homecare nurse, the HCP and homecare nurse will follow the instructions in the protocol and/or the homecare manual (or equivalent document) regarding sample collection, storage, and shipment.

Shipping of Milk Samples

The following instructions are recommended unless they differ from the site's standard operating procedures for labeling, packaging, or shipping of pharmacokinetic samples.

1. Biological samples (ie, milk) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.
   a) SET 1 samples should be shipped directly to CCI [redacted], for analysis per protocol shipping instructions.
   b) When collected by the homecare nurse or HCP, duplicate samples (SET 2) are to be shipped to the study site for storage and shipment to CCI [redacted] per shipping instructions.
2. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
3. Separate the duplicate SET 2 samples from the SET 1 samples.
4. Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc) containing additional absorbent material.

5. Using a permanent marker, write the subject ID, sample matrix (ie, breast milk), number of samples, and "SET 1" on each self-sealing bag.
6. Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 3 through 6 above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2."
7. An inventory of individual samples should accompany each shipment and should include the Sponsor's name (Takeda), study medication (Vedolizumab), protocol number (Vedolizumab-4001), investigator's name, sample type (ie, milk), subject ID, nominal collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.
8. For sample packing, utilize dry ice generously (eg, 20-25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a Styrofoam container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
9. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the Styrofoam container. Place the lid on the Styrofoam container and seal completely with strapping tape. Place the Styrofoam container in a cardboard shipping carton and seal securely with strapping tape.
10. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
11. The investigative site will ship samples to CCI using the lab carton (kit) provided.
12. When shipping samples to CCI affix an address label to each shipping carton. Complete the address label with the following information:

    For Vedolizumab Milk Analyses for PK:

    CCI [redacted]

Affix a carbon dioxide label on each carton, specifically:

Carbon Dioxide Solid UN-1845
Class 9 PKG GR III
Quantity _____
(fill in weight to nearest lb/kg and specify unit of measure used)

13. Affix 2 dry ice symbol labels on opposite sides of the carton. Mark **KEEP FROZEN** on each carton. Specify a return address and contact person on the carton.
14. Obtain the airway bill number and a receipt of shipment from the carrier.
15. After shipping the samples, **please contact Sample Coordinator at** CCI **by phone:** CCI [redacted] them of next day

Name of courier or transport company
Time and date the shipment left the clinical site
Airway bill number

Appendix F Detailed Description of Amendments to Text

Change 1: Updated the Takeda responsible medical officer.

The primary change occurs in Section 1.1 Contacts:

Initial wording:	PPD
Amended or new wording:	PPD

Rationale for Change:

Change made to Takeda responsible medical officer for the study.

Section 1.2 Approval also contains this change.

Change 2: Changed the minimum number of sites and allowed for sites outside of the United States.

The primary change occurs in Section 2.0 STUDY SUMMARY:

Initial wording:	**Number of Sites:** approximately 8 to 10 US
Amended or new wording:	**Number of Sites:** approximately ~~8~~7 to 10 ~~US~~

Rationale for Change:

Allows for additional sites outside of the United States.

Change 3: Updated background information.

The primary change occurs in Section 4.1 Background:

Initial wording:	The effectiveness and safety of vedolizumab intended for intravenous (IV) use (vedolizumab IV, vedolizumab for injection, for intravenous use) for ulcerative colitis (UC) and Crohn's disease (CD) have been established in pivotal phase 3 clinical studies in subjects who had not responded adequately to corticosteroids, immunomodulators, or tumor necrosis factor-alpha (TNF-α) antagonists. As of 19 May 2015, a total of 8 phase 1 studies in healthy subjects, 8 phase 1b/phase 2 studies in subjects with UC or CD, and 3 phase 3 studies in subjects with UC or CD

	have been completed. Eight clinical studies are currently ongoing in the vedolizumab development program. As of 19 May 2015, approximately 3600 subjects (309 healthy subjects, 1393 subjects with UC, and 1896 subjects with CD) have received at least 1 dose of vedolizumab across completed and ongoing studies (see Investigator's Brochure, Edition 18). Vedolizumab exposure has extended for ≥12 months in 1667 subjects, ≥24 months in 1306 subjects, ≥36 months in 935 subjects, ≥48 months in 676 subjects, ≥60 months in 267 subjects, and ≥72 months in 26 subjects. Based on drug shipment data, the cumulative patient exposure to vedolizumab since its marketing approval in May 2014 is estimated to be approximately 11,943 patient-years as of 19 May 2015.
Amended or new wording:	The effectiveness and safety of vedolizumab intended for intravenous (IV) use (vedolizumab IV, vedolizumab for injection, for intravenous use) for ulcerative colitis (UC) and Crohn's disease (CD) have been established in pivotal phase 3 clinical studies in subjects who had not responded adequately to corticosteroids, immunomodulators, or tumor necrosis factor-alpha (TNF-α) antagonists. As of 19 ~~May 2015~~**November 2016**, a total of 8 phase 1 studies in healthy subjects, 8 phase 1b/phase 2 studies in subjects with UC or CD, and 3 phase 3 studies in subjects with UC or CD have been completed. Eight clinical studies are currently ongoing in the vedolizumab development program. As of 19 ~~May 2015~~**November 2016**, approximately ~~3600~~**4200** subjects (309 healthy subjects, ~~1393~~**1811** subjects with UC, ~~and 1896~~**2138** subjects with CD, **3 subjects undergoing allo-HSCT, 1 subject with pouchitis, and 2 subjects with melanoma**) have received at least 1 dose of vedolizumab across completed and ongoing **company-sponsored interventional clinical** studies ~~(see Investigator's Brochure, Edition 18)~~. Vedolizumab exposure **in interventional clinical studies** has extended for ≥12 months in ~~1667~~ **1832** subjects, ≥24 months in ~~1306~~**1379** subjects, ≥36 months in ~~935~~**1169** subjects, ≥48 months in ~~676~~**862** subjects, ≥60 months in ~~267~~**645 subjects, ≥72 months in 308 subjects, ≥84 months in 32** subjects, and ~~≥72 months in 26 subjects.~~**96 months in 22 subjects. Approximately 450 subjects with UC or CD have received at least 1 dose of vedolizumab across ongoing company-sponsored noninterventional clinical studies.** Based on drug shipment data **as of 19 November 2016**, the cumulative **postmarketing** patient exposure to vedolizumab ~~since its marketing approval in May 2014~~IV **globally** is estimated to be approximately ~~11,943~~**77,382** patient-years~~as of 19 May 2015~~.
Rationale for Change:	Background updated to align with the current IB, version 19.

Change 4: Updated inclusion Criterion 7.

The primary change occurs in Section 7.1 Inclusion Criteria:

Initial wording:	The subject was on established vedolizumab maintenance therapy (received at least two 300 mg vedolizumab IV Q8W doses prior to the delivery of infant and one 300 mg Q8W dose of vedolizumab postpartum), which has been commenced by the subject's treating physician for the treatment of active UC or CD prior to enrolling in this study.
Amended or new wording:	The subject **is**~~was~~ on established vedolizumab maintenance therapy ~~(received at least two 300 mg vedolizumab IV Q8W doses prior to the delivery of infant and one 300 mg Q8W dose of vedolizumab postpartum)~~ **and received at least 1 dose of 300 mg of vedolizumab IV postpartum or has completed vedolizumab induction therapy (300 mg of vedolizumab IV at Week 0, Week 2, and Week 6)**, which has been commenced by the subject's treating physician for the treatment of active UC or CD prior to enrolling in this study.

Rationale for Change:

Patients are on an established vedolizumab regimen Q8 weeks or an alternate dose frequency.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY.

Section 6.1 Study Design.

Section 6.2 Justification for Study Design, Dose, and Endpoints.

Change 5 Updated inclusion Criterion 7.

The primary change occurs in Section 7.1 Inclusion Criteria:

Initial wording:	The subject is at least 6 weeks postpartum by Day 1.
Amended or new wording:	The subject is at least ~~6~~**5** weeks postpartum by Day 1.

Rationale for Change:

Revised time is sufficient to exclude colostrum phase in patients on an established vedolizumab regimen who have received 1 dose prior to Day 1.

Change 6: Removed exclusion Criterion 3.

The primary change occurs in Section 7.2 Exclusion Criteria:

Deleted text: ~~3. The subject is expected to receive additional vedolizumab treatment between Day 2 and Study Exit/Follow-up (Day 57).~~

Rationale for Change:

Patients in this study are on an established vedolizumab regimen.

Change 7: Removed exclusion Criterion 4.

The primary change occurs in Section 7.2 Exclusion Criteria:

Deleted text: ~~4. The subject has received natalizumab treatment.~~

Rationale for Change:

Patients in this study are on an established vedolizumab regimen, and prior natalizumab use is not prohibited in the approved vedolizumab label.

Change 8: Removed the electrocardiogram (ECG) procedure.

The primary change occurred in Section 9.1.13 (section deleted):

Deleted text:

~~9.1.13 ECG Procedure~~

~~Standard 12-lead ECGs will be recorded at Screening and at Study Exit/Follow-up (Day 57 [±3]) or Early Termination. Single ECGs will be taken at Screening and Day 57 (±3)/Early Termination visits. Additional unscheduled ECGs may be recorded where clinically necessary for subject safety.~~

~~When an ECG is scheduled at the same time as milk collection or vital signs then the milk collection and vital signs will take priority and the ECG will be obtained before or after the scheduled milk collection/vital sign assessment. If an ECG coincides with a meal, ECG will take precedence followed by the meal.~~

~~All stationary 12-lead ECG machines will be supplied by the site. Subjects should be in a supine position following an approximate 10-minute rest period for ECG recordings. Should technical difficulties occur during recording of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.~~

~~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. Paper ECG traces will be recorded for 10 seconds at a standard paper speed of 25 mm/sec and gain of 10 m/mV or digital recordings will be used.~~

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

Rationale for Change:

There is no therapeutic intervention for this study, and subjects are on an established vedolizumab regimen. Enhanced monitoring by ECG is not required in the approved vedolizumab labeling.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY.

Section 3.3 List of Abbreviations.

Section 5.2.3 Safety Endpoints for Lactating Women.

Section 7.2 Exclusion Criteria.

Section 9.1.8 Documentation of Concurrent Medical Conditions.

Section 10.1.3 Additional Points to Consider for PTEs and AEs.

Section 13.1.4.3 ECGs (section deleted).

Appendix A Schedule of Study Procedures.

Change 9: Removed all clinical laboratory tests (hematology, serum chemistry, urine drug screen, and urinalysis), except for the urine pregnancy test (human chorionic gonadotropin [hCG]) for women of childbearing potential.

The primary change occurs in Section 9.1.9 Procedures for Clinical Laboratory Samples.

Deleted text:

~~All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 20 mL. The approximate total volume of blood for the study is 60 mL.~~

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

~~Table 9.a Clinical Laboratory Tests~~

~~Hematology~~	~~Serum Chemistry~~	~~Urinalysis~~
~~RBCs~~	~~Alanine aminotransferase~~	~~pH~~
~~WBCs with differential~~	~~Albumin~~	~~Specific gravity~~
~~Hemoglobin~~	~~Alkaline phosphatase~~	~~Protein~~
~~Hematocrit~~	~~Aspartate aminotransferase~~	~~Glucose~~
~~Platelets~~	~~Total bilirubin~~	~~Blood~~
~~PT/INR (a)~~	~~Total protein~~	~~Nitrite~~
	~~Creatinine~~	
	~~Blood urea nitrogen~~	~~Microscopic Analysis*:~~
	~~Creatine kinase~~	~~RBC/high power field~~
	~~γ-Glutamyl transferase~~	~~WBC/high power field~~
	~~Potassium~~	~~Epithelial cells, casts etc~~
	~~Sodium~~	
	~~Glucose~~	
	~~Chloride~~	
	~~Bicarbonate~~	~~*To be performed if abnormal~~
	~~Calcium~~	
	~~Amylase (b)~~	
	~~C-reactive protein~~	

~~Diagnostic Screening:~~	
~~Serum~~	~~Urine~~
~~Hepatitis panel, including HBsAg and anti-HCV~~	~~Drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, alcohol and opiates.~~
	~~hCG (b)~~

~~hCG= human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cell.~~
~~(a)To be performed at Screening and Study Exit/Follow-up (Day 57 [±3]).~~
~~(b) To be performed at Screening, on Day 1 prior to dosing and on Study Exit/Follow-up (Day 57 [±3])/Early Termination prior to the next scheduled dose.~~

~~The central 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. All laboratory safety data will be transferred electronically to Takeda or designee in the format~~

~~requested by Takeda. 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 PI or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.~~

~~All clinically significant laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. 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.~~

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

~~Please refer to Section 7.7 for discontinuation criteria, and Section 10.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3×ULN in conjunction with total bilirubin >2×ULN.~~

~~If the ALT or AST remains elevated >3×ULN on these 2 consecutive occasions, the subject should return to their treating physician for management and additional testing and close monitoring. The abnormality should be recorded as an AE and follow-up information provided (please refer to Section 10.3 Reporting of Abnormal Liver Function Tests for reporting requirements).~~

Amended or new wording: **A urine pregnancy test (human chorionic gonadotropin [hCG]) will be performed at Screening, on Day 1 prior to dosing, and on Day 57 prior to the next scheduled dose.**

Rationale for Change:

There is no therapeutic intervention for this study and subjects are on an established vedolizumab regimen. Enhanced screening and monitoring by clinical laboratory assessments is not required in the approved vedolizumab labeling.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY.

Section 3.3 List of Abbreviations.

Section 5.2.3 Safety Endpoints for Lactating Women.

Section 7.2 Exclusion Criteria.

Section 9.1.9 Procedures for Clinical Laboratory Samples.

Section 9.4 Blood Volume (deleted section).

Appendix A Schedule of Study Procedures.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	25-Jul-2017 19:42 UTC
	Clinical Pharmacology Approval	25-Jul-2017 19:42 UTC
	Statistical Approval	25-Jul-2017 19:49 UTC
	Clinical Science Approval	26-Jul-2017 01:03 UTC