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

SAP Approve Date: 5 March 2018

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

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

TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: VEDOLIZUMAB-4001

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

Version: 1.0

Date: 5 March 2018

Prepared by:

PPD

Prepared by:

PPD

1.0 APPROVAL SIGNATURES

Study 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

PPD

2.0 TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_t	area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
AUCτ	Area under the milk concentration-time curve during a dosing interval (τ).
BLQ	below the limit of quantification
BMI	body mass index
C_{max}	maximum observed plasma concentration
CD	Crohn's Disease
eCRF	electronic case report form
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
PML	progressive multifocal leukoencephalitis
PT	preferred term
PTE	pretreatment event
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
UC	Ulcerative Colitis
WHODrug	World Health Organization Drug Dictionary

3.0 OBJECTIVES

3.1 PRIMARY OBJECTIVE

To assess the concentration of vedolizumab in breast milk of lactating women with active Ulcerative Colitis (UC) or Crohn's Disease (CD) who are receiving vedolizumab IV therapeutically.

3.2 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.

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 1.

Table 1 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 presented in Table 2.

Table 2 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)

A schedule of assessments is listed in Protocol Vedolizumab-4001[1].

4.0 ANALYSIS ENDPOINTS

4.1 PRIMARY ENDPOINT

The primary endpoint of this study is the 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).

4.2 OTHER ENDPOINT

- Area under the milk concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_t), area under the milk concentration-time curve during a dosing interval (AUC_τ), maximum observed milk concentration (C_{max}) and time to reach 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.

4.3 SAFETY ENDPOINT

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

5.0 DETERMINATION OF SAMPLE SIZE

The sample size of 10 to 12 subjects is considered to be sufficient for this milk-only lactating 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.

6.0 METHODS OF ANALYSIS AND PRESENTATION

6.1 GENERAL PRINCIPLES

All study-related raw data, including derived data, will be presented in data listings.

Continuous data will be summarized using: number of subjects (N), arithmetic mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Arithmetic mean, and median will be formatted to one more decimal place than the measured value. The standard deviation (SD) will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value. Confidence intervals about a parameter estimate will be presented to the same decimal places as the parameter estimate. Where indicated, coefficient of variation (%CV) and geometric mean will also be included in the summary of continuous data.

Categorical data will be summarized using the number and percentage of subjects for each category where appropriate.

6.1.1 MISSING DATA

There will be no imputation of incomplete or missing data unless specified otherwise. Decisions regarding inclusion or exclusion of data from an analysis for subjects who are noncompliant with the dose schedule, or who have incomplete data, will be made on a case-by-case basis, but the data will be presented in data listings regardless.

Concentrations of vedolizumab in breast milk that are below the limit of quantification (BLQ) will be treated as zero in the summarizing concentration values and deriving of PK parameters. These values will be flagged in the data listings, and deviations from this convention may be considered on a case-by-case basis as deemed appropriate.

6.1.2 DERIVED DATASETS AND VARIABLES

Derived datasets will be generated according to CDISC guidance documents: Analysis Data Model (ADaM) Implementation Guide, Version 1.1 (12 Feb 2016); ADaM Data Structure for Adverse Event Analysis, Version 1.0 (10 May 2012). Following are definitions of derived variables:

- Body mass index (BMI) will be calculated as weight (kg)/(height (m))^2 and will be presented to 1 decimal place. BMI will be calculated for Screening.
- Age is calculated by (date of informed consent – date of birth + 1) / 365.25.

6.1.3 DEFINITION OF STUDY DAYS AND BASELINE

For all safety endpoints, baseline is defined as the last non-missing measurement prior to first dose of vedolizumab. Study day will be calculated relative to the date of the first dosing. Study day prior to the first dose of treatment will be calculated as: date of assessment/event – date of first dose of treatment; study day on or after the date of first dose of treatment will be calculated as: date of assessment/event – date of first dose of treatment + 1.

6.2 ANALYSIS SETS

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

6.3 DISPOSITION OF SUBJECTS

The primary reason for screen failure will be summarized.

Number and percentage of subjects who complete vedolizumab, prematurely discontinue vedolizumab will be summarized. In addition, the number and percentage of subjects will be summarized for each reason of discontinuation of vedolizumab. Subjects' study completion data, including reasons for premature termination, will be listed for all subjects.

The number and percentage of subjects who comprised each analysis set will be summarized.

The number and percentage of subjects with at least 1 significant protocol deviation, and the number and percentage of subjects within each deviation category captured on the electronic case report form (eCRF) will be summarized based on safety population.

6.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics to be obtained will include age, gender, race, ethnicity, height, weight, alcohol use, smoking status, reproductive status, and lactation history. Summary statistics (number of subjects [N], mean, SD, median, minimum, and maximum) will be generated for continuous variables, and the number and percentage of subjects within each category will be presented for categorical variables using the safety set.

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. Overall listing will be provided to support the tables.

6.5 MEDICAL HISTORY AND CONCURRENT MEDICAL CONDITIONS

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. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. The medical history and concurrent medical conditions will be presented in the listing with coded system organ class (SOC) and preferred term (PT) using the latest Medical Dictionary for Regulatory Activities (MedDRA) for the safety set.

6.6 MEDICATION HISTORY AND CONCOMITANT MEDICATION

Medication history includes any medication relevant to eligibility criteria stopped at or within 60 days prior to signing of informed consent. Concomitant medication is any medication other than the study medication, and used from signing of informed consent through the end of the study. All non-study medication will be coded by World Health Organization Anatomical Therapeutic Chemical (ATC) code and PT using the latest World Health Organization Drug Dictionary (WHO Drug).

Overall listing will also be provided to include dose, unit, frequency, route of administration, start and end dates, and reason for use for the safety set.

Conventions for Missing Concomitant Medication Dates

Start and stop dates for medication history and concomitant medications are collected on the eCRF. Definitions of medication history and concomitant medications are defined in Section 7.6. Missing or partial dates for medication history will not be imputed. However, in case of missing or partial dates for concomitant medications and information is not available for whether unknown end date is prior or after informed consent date or ongoing, the following rules will be used:

If the start date is partial or unknown:

- If the day is missing, the start day will be the first day of the month
- If the month is missing, the start month will be the month corresponding to 90 days prior to the date of first dose of vedolizumab
- If the year is missing, the start year will be the minimum of the year of the first clinic visit or the year of the informed consent date
- If the entire date is unknown, the start date will be the date of first dose of vedolizumab.

If the stop date is partial, unknown or "ongoing":

- If the day is missing, the stop day will be the last day of the month reported
- If the month is missing, the stop month will be to the month during which the last assessment occurred
- If the year is missing or the entire date is unknown or if the medication is "ongoing", the stop year will be the year in which the last assessment occurred.

6.7 VEDOLIZUMAB EXPOSURE AND COMPLIANCE

IV infusion date and time, the volume infused, and reason for not being able to infuse the total amount will be listed. No other summary statistics for the extent of exposure to vedolizumab or compliance calculations will be performed for this study.

6.8 EFFICACY ANALYSIS

Not applicable.

6.9 PHARMACOKINETIC ANALYSIS

6.9.1 MILK CONCENTRATIONS OF VEDOLIZUMAB

Milk from each breast will be completely emptied using an electric milk pump at the specified time points (per 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 on the source document and eCRF. 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.

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

Concentrations of vedolizumab in milk will be summarized by scheduled time points using descriptive statistics (N, mean, SD, %CV, median, minimum, and maximum) for the PK set. Individual milk concentration versus time data will be presented in a data listing.

6.9.2 MILK PHARMACOKINETIC PARAMETERS OF VEDOLIZUMAB

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 AUCτ values and the standardized breast-fed infant milk consumption of 150 mL/kg/day per FDA guidance on clinical lactation studies, as appropriate. Additional PK parameters may be calculated.

Symbol/Term	Definition
Milk	
AUC_t	Area under the milk concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_τ	Area under the milk concentration-time curve during a dosing interval (τ).
C_{max}	Maximum observed milk concentration.
t_{max}	Time to reach 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 x 150 mL/kg/day (daily dosage on the corresponding sampling day) or AUC_τ/τ x 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 x τ / Weight-adjusted Maternal Dosage × 100

Milk PK parameters of vedolizumab will be summarized using descriptive statistics (N, mean, SD, %CV, median, minimum, and maximum) for the PK set. Geometric means will be provided for C_{max} and AUCs.

Individual milk pharmacokinetic parameters will be presented in a data listing.

6.10 Other Outcomes

Not applicable.

6.11 Safety Analysis

All safety summary tables will be presented for all subjects in the safety set.

6.11.1 Adverse Events

A pretreatment event (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. A treatment emergent adverse event (TEAE) is defined as an adverse event with onset occurring within 57 days after vedolizumab administration. Adverse event verbatim reported terms will be coded by system organ class (SOC) and preferred term (PT). 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.

TEAE summary tables will include numbers and percentages of subjects experiencing at least one AE by SOC and PT. The following is a list of AE summary tables to be generated:

- Overview of TEAE.
- TEAEs by SOC and PT.
- Subject Mapping of TEAEs by SOC and PT.
- Most Frequent TEAEs by PT.
- Relationship of TEAEs to vedolizumab by SOC and PT.
- Drug-Related TEAEs by SOC and PT.
- Intensity of TEAEs by SOC and PT.

- Intensity of Drug-Related TEAEs by SOC and PT.
- Serious TEAE.
- AE of special interest.

Additional AE summary tables may be added as appropriate.

A subject with 2 or more different adverse events within the same level of the MedDRA term will be counted only once in that level using the most extreme incident (most severe for the intensity tables, and related for the relationship to vedolizumab tables).

Most frequent TEAEs are defined as the adverse events occurring in at least 2 or more subjects. If the severity level of an AE is missing, the severity of AE will be considered as severe. If the relationship of an AE is missing, the AE will be considered related to vedolizumab.

Data listings will be provided for all adverse events (including AEs with onset dates before the start of study medication or 57 days after last dose of study medication), adverse events leading to vedolizumab discontinuation, SAEs, and AEs resulting in death.

The adverse events of special interest and definitions are listed below:

Special Interest Events	MedDRA Terms or Definitions
Gastrointestinal Events	SOC: GASTROINTESTINAL DISORDERS
Malignancies	SOC: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)
Infections	SOC: INFECTIONS AND INFESTATIONS
Infusion Related Reactions	Analysis for these AEs will occur on two levels: • Investigator defined Infusion Related Reactions (as indicated on the AE CRF). • All AEs that occur on or one calendar day after the infusion date.
Injection site reaction	Injection Site Reaction (HLT)
Hypersensitivity Reactions	Anaphylactic/anaphylactoid shock conditions SMQ (broad). Angioedema SMQ (broad). Hypersensitivity SMQ (broad).
Progressive Multifocal Leukoencephalitis (PML)	Human polyomavirus infection PT. JC virus infection PT. JC virus test positive PT. Leukoencephalopathy PT. Polyomavirus test positive PT. Progressive multifocal leukoencephalopathy PT.
Liver injury	Cholestasis and jaundice of hepatic origin SMQ (Broad) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (Broad) Hepatitis, non-infectious SMQ (Broad) Liver related investigations, signs and symptoms SMQ (Narrow) Liver infections SMQ (Broad)

The number and percentage of subjects with at least 1 treatment emergent AE of special interest, and the number and percentage of subjects by SOC and PT within each special interest listed above will be summarized.

Conventions for Missing Adverse Event Dates

Every effort will be made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator.

For AEs or SAEs, if the type of Pretreatment Event/Adverse Event was not determined on eCRF, a missing or incomplete onset date will be imputed according to the following conventions:

1) If an onset date is missing, the derived onset date will be calculated as the first non-missing valid date from the following list (in order of precedence):

- First study medication date
- Consent date (for SAEs only)

2) If an onset date is incomplete, the derived onset date will be calculated following:

- Missing day, but month and year present: the day will be imputed as the 15th of the month. If the month and year are equal to the month and year of the first study medication dose and the first study medication dose occurs after the imputed date, the derived onset date will be set equal to the first study medication date. If the AE end date occurs prior to the imputed date, the derived onset date will be set equal to the AE end date.
- Missing day and month, but year present: the day and month will be imputed as the 30th June of the year. If the year is equal to the year of the first study medication dose and the first study medication dose occurs after the imputed date, the derived onset date will be set equal to the first study medication date. If the AE end date occurs prior to the imputed date, the derived onset date will be set equal to the AE end date.
- If the imputed AE onset date occurs after the database lock date, the imputed AE onset date will be imputed as the database lock date.

For AEs or SAEs, a missing or incomplete end date will be imputed according to the following conventions:

1) If an end date is missing, the derived end date will be imputed as the last assessment date, assuming that the last assessment occurs after the AE start. If the last assessment occurs prior to the AE start date, the derived end date will be imputed as the AE start date.

2) If an end date is incomplete, the derived end date will be calculated following:

- Missing day, but month and year present: the day will be imputed as the last date (for example February 2009 will be imputed as 28 February 2009) of the month.
- Missing day and month, but year present: the day and month will be imputed as the 31st December of the year.
- If the imputed AE end date occurs after the database lock date, the imputed AE end date will be imputed as the database lock date.

6.11.2 VITAL SIGNS

Vital sign measurements include oral temperature, pulse, respiration rate, and blood pressure.

Descriptive statistics (N, mean, median, SD, minimum and maximum) of these vital signs will be summarized for baseline, post-dosing, and change from baseline at each visit. Only the vital signs collected at the scheduled visits or time points will be included in the summary. No statistical tests will be performed for the observed vital signs.

All individual vital signs that meet Takeda's predefined criteria for markedly abnormal values (Appendix A) will be listed. The number and percentage of subjects with at least one post dose markedly abnormal vital sign measurement will be summarized and subject mapping presented in a table. All post dose vital signs including both scheduled and unscheduled measurements, will be included in the MAV summaries.

6.11.3 OTHER OBSERVATIONS RELATED TO SAFETY

Other assessments, for example urine pregnancy test, PML, physical examination, etc. will be presented in the listings.

6.12 INTERIM ANALYSIS

No interim analysis is planned.

6.13 CHANGES IN THE STATISTICAL ANALYSIS PLAN

No change in the statistical analysis plan.

7.0 REFERENCES

1. Protocol Amendment 2: An Open-Label, Multicenter, 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. 25 July 2017.

Appendix A Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	°C	< 35.6	>37.7
	°F	<96.1	>99.9

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[redacted]

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