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

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Vedolizumab-1014

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

PHASE 1

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{∞}	area under the serum concentration-time curve from time 0 to infinity
AUC_{last}	area under the serum concentration-time curve from time 0 to time of the last measurable concentration
AVA	anti-vedolizumab antibody
Cmax	maximum observed serum concentration
CPK	creatine phosphokinase
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
GGT	γ-glutamyl transferase
IV	intravenous
LLN	lower limit of normal
LTFU	long-tern follow-up
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PTE	pretreatment event
SAE	serious adverse event
SD	standard deviation
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objective

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

4.2 Secondary Objective

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

4.3 Study Design

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

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

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

A schematic of the study design is included as Figure 4.a.

Figure 4.a Schematic of Study Design

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

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

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

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

5.2 Secondary Endpoints

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

5.3 Safety Endpoints

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

5.4 Additional Endpoints

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

6.0 DETERMINATION OF SAMPLE SIZE

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

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Baseline values are defined as the last observed value before dosing of study medication.

All statistical analyses will be conducted using SAS® Version 9.4, or higher.

All confidence intervals, statistical tests, and resulting P-values will be reported as 2-sided and will be assessed at α=0.05 significance level unless otherwise stated. P-values will be rounded to 3 decimal places prior to assessment of statistical significance.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

Screen failure subjects will be grouped and listed at the end.

7.1.1 Study Definitions

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the medication. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.3 Definition of Study Visit Windows

A windowing convention will be used to determine the analysis value for a given study visit that applies to observed data. For each visit, a window will be defined such that the lower and upper bounds of each window is generally the midpoint between 2 consecutive study visits.

More than 1 result for a parameter may be obtained in a visit window. In such an event, the result with the date closest to the scheduled visit day will be used. In the event of 2 observations equidistant to the scheduled visit day, the later of the observations will be used.

Figure 7.a Study visits

Visit	Scheduled Visit Day	Visit Window (Days)					
		Vital Signs	ECG	Labs	AVA	PK	Safety Survey
	10	9-11			9-11	9-11	
	15	14-16				14-16	
	29	27-31		27-31	27-31	27-31	
	43	41-45			41-45	41-45	
	64	61-67			61-67	61-67	
	85	82-87		82-87	82-87	82-87	
	106	103-109			103-109	103-109	
Final Visit	127	124-130	124-130	124-130	124-130	124-130	
LTFU Safety Survey	168						165-171

7.1.4 Conventions for Missing Adverse Event Dates

Adverse event (AE) dates that are completely or partially missing will be imputed. The imputed dates will only be used to evaluate the treatment-emergent status as specified in Section 7.11.1. The imputation will be performed on start date first, and then on end dates for each record of AE.

7.1.4.1 Impute Incomplete or Missing Start Dates

1. If the start date has non-missing month and year but day is missing.
   a) Impute the AE start date as 15th day of the month.
   b) If the combination of year and month is the same as the year and month of first dose date, impute the AE start date as the later of (first dose date, 15th day of the month).
2. If the start date has non-missing year, but day and months are missing.
   a) Impute the AE start date as June 15th of the year.
   b) If the year is the same as the year of first dose date, impute the AE start date as the late of (first dose date, June 15th of the year).
3. If the start date is completely missing, the impute AE start date as.
   a) First dose date or date of Informed Consent if patient is not dosed.
4. If the imputed AE start date is later than the un-imputed AE end date after steps 1-3, then impute the AE start date the same as the AE end date.
5. If the imputed AE start date is later than the database cutoff date after steps 1-4, then impute the AE start date the same as the database cutoff date.

7.1.4.2 Impute Incomplete or Missing End Dates

1. If the AE end date has month and year, but day is missing, impute the date the last day of the month (for example, February 2018 will be imputed as 28 February 2018).
2. If the AE end date has year, but month and day is missing, impute the date as the last day of the year (i.e. December 31st of the year).
3. If the AE end date is completely missing, impute the date as the last assessment date of the subject.
4. If the imputed AE end date is earlier than the AE start date (imputed version) after steps 1-3, then impute the AE end date the same as the AE start date (imputed version).
5. If the imputed AE end date is later than the database cutoff date after steps 1-4, then impute the AE end date the same as the database cutoff date.

7.1.5 Conventions for Missing Concomitant Medication Dates

Start and stop dates for all prior and concomitant medications, and start date for concomitant procedures are collected on the eCRF. Dates for prior concomitant medication and procedures that are completely or partially missing will be imputed. The imputation will be performed on start date first, and then on end dates for each record of medication as follows

7.1.5.1 Impute for Incomplete or Missing Start Dates of Medication or Procedure

1. If the day is missing, the start date will be the first day of the month.
2. If the month is missing, the start month will be the month corresponding to 90 days prior to the date of first dose of study drug.
3. If the year is missing, the start year will be the minimum of (the year of the first clinic visit, the year of the informed consent date).
4. If the entire date is unknown, the start date will be the date of first dose of study drug.

7.1.5.2 Impute for Incomplete or Missing End Dates of Medication

1. If the day is missing, the stop day will be the last day of the month reported.
2. If the month is missing, the stop month will be to the month during which the last assessment occurred.
3. 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.

No dates will be imputed for previous medications.

7.2 Analysis Sets

Safety Set:

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

Pharmacokinetic Set:

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

7.3 Disposition of Subjects

Disposition of all subjects in the Safety Set will be tabulated:

- All subjects received study drug (denominator).
- Subjects who completed the study.
- Subjects who prematurely discontinued study treatment.
- Subjects who prematurely discontinued study.

Primary reasons for discontinuation of study treatment or study will be entered on the electronic case report form (eCRF), will be tabulated. Reasons for premature discontinuation of study an and/or study treatment include death, adverse event, protocol deviation, lost to follow-up, withdrawal by subject, study termination by sponsor, pregnancy, and other. The date of dosing and the reason for premature discontinuation of study drug/study visit will be presented for each subject in listings.

Disposition of screen failure subjects will be summarized descriptively, as described in Section 7.4.

7.4 Demographic and Other Baseline Characteristics

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

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

7.5 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. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening examination.

Medical history and concurrent medical conditions will be coded using MedDRA and will be separately summarized by system organ class and preferred term. They will also be presented in data listings.

7.6 Medication History and 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.

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

Prior and concomitant medications will be summarized by drug class (ATC Pharmacological subgroup), WHODrug preferred term. All prior and concomitant medications will be listed.

Concomitant procedures will not be coded, but will be presented in listings as appropriate.

7.7 Study Drug Exposure and Compliance

The single dose of study medication will be administered while subjects are under observation in the clinical research unit. The date and time of the single dose will be recorded, as well as any dose adjustment (drug withdrawn, drug infusion interrupted) and the reason for it These results will be listed and summarized.

7.8 Efficacy Analysis

Not applicable

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Descriptive statistics will be used to summarize serum concentrations of vedolizumab over each scheduled sampling time. Individual serum concentration-time data will be presented as listings. Additionally, graphical plots of individual and mean plasma concentration vs time profiles will be presented (untransformed and semi-log scales).

The PK parameters of vedolizumab will be determined from the concentration-time profiles for all evaluable subjects using a non-compartmental analysis method. The PK parameters, including

t_{max}, C_{max}, AUC_{last}, AUC_{∞}, V_z, CL and $t_{1/2z}$, will be determined from serum concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

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

Serum concentrations 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.

7.9.2 Pharmacodynamic Analysis

Not applicable

7.10 Immunogenicity Analysis

Titers of AVA and neutralizing AVA will be listed. The following tables for immunogenicity analysis will be produced:

- Summary of AVA status.
- Summary of AVA status by study visit.
- Summary of AVA status by titer.

In addition, the impact of AVA on PK and safety may be explored.

7.10.1 AVA Definitions

1. Definition of AVA positive and negative
    - **Negative AVA**: defined as a sample that was evaluated as negative in the AVA screening assay. Samples that were determined to be positive in the AVA screening assay but the result was not confirmed in the AVA confirmatory assay were considered negative.
    - **Positive AVA**: defined as a sample that was evaluated as positive in both the AVA screening and confirmatory assays.
    - **Positive neutralizing AVA**: defined as a sample that was evaluated as positive in the neutralizing AVA assay.

Subject AVA status will be grouped into 3 categories as follows:

- **Negative**: defined as subjects who did not have confirmed AVA results.
- **Positive**: defined as subjects who had at least 1 positive AVA result.
    - Transiently positive: defined as subjects with confirmed positive AVA in 1 sample.
    - Persistently positive: defined as subjects with confirmed positive AVA in 2 or more consecutive positive AVA samples.

- Subject AVA positive at baseline is defined as a positive AVA sample at Week 0 (predose).

7.11 Safety Analysis

7.11.1 Adverse Events

7.11.1.1 Definitions

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. 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. A treatment-emergent adverse event (TEAE) is defined as AE which occurs upon or after dosing with study drug, up to day 130.

Adverse events of special interest (AESIs) for vedolizumab include serious infections (including opportunistic infection such as PML), liver injury, malignancies, infusion-related or systemic reactions and hypersensitivity.

7.11.1.2 Analysis and Reporting

The number and percentage of subjects with TEAEs, AESIs for vedolizumab, and serious adverse, which occur on or after dosing in patients, will be summarized by MedDRA system organ class, and preferred term overall, by severity, and by relationship to study drug. Separate summaries will also be generated for treatment-related AEs overall and by severity. Data listings will be provided for all AEs (including PTEs for enrolled subjects), AEs leading to study drug discontinuation, AEs leading to study visit discontinuation, SAEs, AESIs, and AEs resulting in death. The Medical Dictionary for Regulatory Activities (MedDRA v20.1 or higher) will be used for coding AEs.

7.11.2 Clinical Laboratory Evaluations

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

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to System International (SI) units. If a lab value is reported using a non-numeric qualifier (e.g., less than ($<$, $\leq$) a certain value, or greater than ($>$, $\geq$) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

Laboratory abnormalities will be evaluated based on the markedly abnormal value (MAV) criteria in Appendix A.

7.11.3 Vital Signs

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

See Appendix B for MAV criteria for vital signs.

7.11.4 12-Lead ECGs

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

See Appendix C for MAV criteria for ECGs.

7.11.5 Other Observations Related to Safety

Physical examination findings and PML checklist data will be presented in data listings.

7.12 Interim Analysis

Not applicable

7.13 Changes in the Statistical Analysis Plan

Not applicable

8.0 REFERENCES

Not applicable

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	<0.8 × LLN	>1.2 × ULN
Hematocrit	Both	<0.8 × LLN	>1.2 × ULN
RBC count	Both	<0.8 × LLN	>1.2 × ULN
WBC count	Both	<0.5 x LLN	>1.5 x ULN
Platelet count	Conventional	<75 x 10^3/µL	>600 x 10^3/µL
	SI	<75 x 10^9/L	>600 x 10^9/L

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3x ULN
AST	Both	--	>3x ULN
GGT	Both	--	>3x ULN
Alkaline phosphatase	Both	--	>3x ULN
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 µmol/L
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional	--	>2.0 mg/dL
	SI		>177 µmol/L
Blood urea nitrogen	Conventional		>30 mg/dL
	SI		>10.7 mmol/L
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L
Potassium	Conventional	<3.0 mEq/L	>6.0 mEq/L
	SI	<3.0 mmol/L	>6.0 mmol/L
CPK	Both	--	>5x ULN
Glucose	Conventional	<50 mg/dL	>350 mg/dL
	SI	<2.8 mmol/L	>19.4 mmol/L
Calcium	Conventional	<7.0 mg/dL	>11.5 mg/dL
	SI	<1.75 mmol/L	>2.88 mmol/L

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CPK=creatine phosphokinase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B Criteria 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

Appendix C Criteria for Out-of-Range Values for the 12-Lead ECG Parameters

Parameter	Lower Criteria	Upper Criteria
Heart rate	<50 beats per minute	>120 beats per minute
PR	≤80 milliseconds	≥200 milliseconds
QT Interval	≤300 milliseconds	≥460 milliseconds
QTcB Interval	≤300 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QTcF Interval	≤300 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QRS	≤80 milliseconds	≥180 milliseconds

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	09-Dec-2018 15:08 UTC
	Clinical Pharmacology Approval	09-Dec-2018 23:27 UTC
	Clinical Science Approval	10-Dec-2018 01:22 UTC
	Biostatistics Approval	10-Dec-2018 14:01 UTC