Statistical Analysis Plan: I5T-MC-AACP (v2)

A Phase 1, Open-Label Study to Characterize the Pharmacokinetics of Donanemab Following Intravenous Doses in Healthy Participants

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STATISTICAL ANALYSIS PLAN

A Phase 1, Open-Label Study to Characterize the Pharmacokinetics of Donanemab Following Intravenous Doses in Healthy Participants

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Clinical Phase I

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2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

%AUC(t_{last}-∞)	Fraction of AUC(0-∞) extrapolated
AE	Adverse event
ADA	Anti-drug antibody
AUC	Area under the concentration versus time curve
$AUC_{0\text{-}4weeks}$	Area under the concentration vs time curve from time 0 to 4weeks
$AUC_{0\text{-}2weeks}$	Area under the concentration vs time curve for first dosing interval
AUCτ,ss	Area under the concentration versus time curve during one dosing interval at steady state
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
BQL	Below the quantifiable lower limit of the assay
CL	Total body clearance of drug calculated after intravenous administration
$CL_{,ss}$	Total body clearance of drug calculated at steady state after intravenous administration
C_{last}	Last quantifiable drug concentration
C_{max}	Maximum observed drug concentration
$C_{max,ss}$	Maximum observed drug concentration during a dosing interval at steady state
$C_{min,ss}$	Minimum observed drug concentration during a dosing interval at steady state
CRU	Clinical Research Unit
CSR	Clinical Study Report
CSSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of variation
DMP	Data Management Plan
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
IV	Intravenous

IRR	Infusion related reactions
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
Q2W	Every 2 weeks
RA_{AUC}	Accumulation ratio for $AUC_{\tau,ss}$ at steady state / $AUC_{0\text{-}2weeks}$
RA_{Cmax}	Accumulation ratio for $C_{max,ss}$ at steady state / $C_{max,\ day\ 1}$
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOP	Standard Operating Procedure
TBL	Total bilirubin
TE-ADA	Treatment emergent antidrug antibodies
TEAE	Treatment emergent adverse event
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{max}	Time of maximum observed drug concentration
V_{ss}	Volume of distribution at steady state following intravenous administration
V_z	Volume of distribution during the terminal phase

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 12 December 2022).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to first participant visit. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To characterize the PK profile of donanemab following administration of 350 mg intravenous (IV) doses in healthy participants	• Area under the concentration versus time curve 0 to 4 weeks ($AUC_{0\text{-}4\ Weeks}$) • Maximum observed drug concentration during a dosing interval at steady state ($C_{max,\ ss}$) and • Area under the concentration versus time curve during a dosing interval at steady state ($AUC_{\tau,\ ss}$)
Secondary	
• To investigate the safety and tolerability of donanemab following administration of 350 mg IV doses in healthy participants	• Incidence of treatment-emergent adverse events (TEAE) and serious adverse events (SAE).
Exploratory	
• To assess the effect of treatment-emergent anti-drug antibodies (TE-ADAs) on the PK of 350 mg IV donanemab	• Model parameters for the exposure-response relationship between donanemab serum concentrations and anti-drug antibody (ADA) titer
• To characterize immunogenicity of donanemab following administration of 350 mg IV doses in healthy participants	• Incidence of TE-ADA

5. STUDY DESIGN

This is a Phase 1, open-label study to evaluate the PK, safety, and tolerability of 350 mg donanemab administered as a single IV dose every 2 weeks (Q2W) for 10 weeks in healthy participants. Approximately 40 participants may be enrolled so that approximately 25 participants complete the study. Participants will receive a single 350 mg dose of donanemab Q2W for 10 weeks. After each dose administration, participants will remain in the clinical research unit (CRU) for up to 5 days. Participants will return to the CRU for regular outpatient visits until the next dose of donanemab. These visits will occur on Days 3, 4, 5, and 8 (unless the participant is still admitted to the CRU, in which activities for those days will be performed during the inpatient stay). After the last dose of donanemab, participants will return for outpatient visits up to 12 weeks after the last dose.

Screening may occur up to 28 days prior to enrollment into the study. Once the informed consent is signed by the participants, they will be assessed for eligibility and will undergo screening procedures.

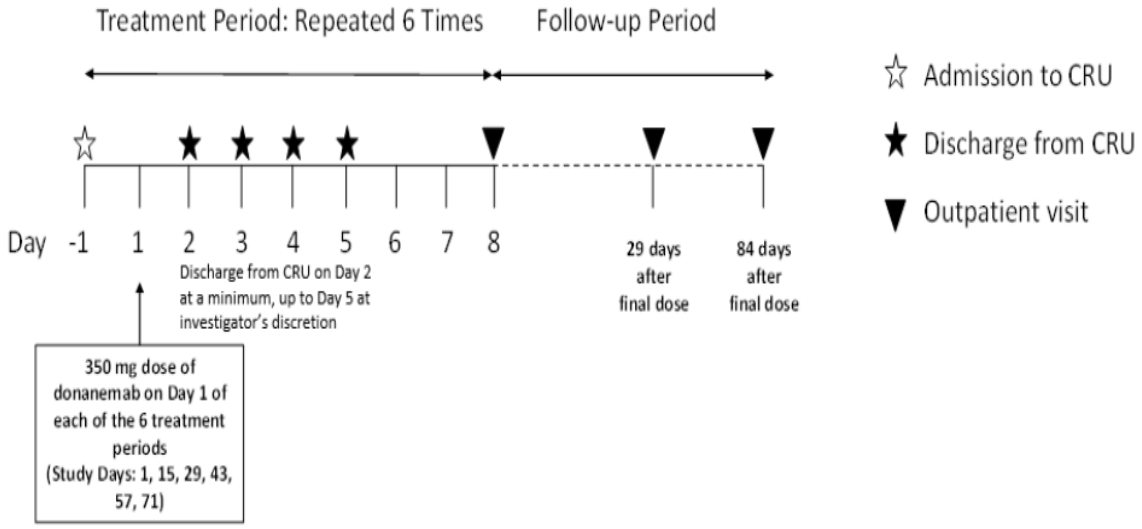
Participants who are not enrolled within 28 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility. Eligible participants will be admitted to the CRU on Day -1 prior to dosing in each of the 6 treatment periods. On Day 1 of

each treatment period, participants will be dosed with an IV dose of donanemab and remain in the CRU until discharge on Day 2, although participants may remain inpatient up to Day 5 of each treatment period at the discretion of the investigator. After dosing with 350 mg donanemab, participants will return to the CRU approximately 2 weeks later to be admitted at Day -1 of the subsequent period.

Safety and tolerability will be assessed through electrocardiograms (ECGs), clinical laboratory tests, vital sign measurements, recording of adverse events (AEs), physical examination, and neurological examination. Additionally, immunogenicity will be assessed.

After discharge from the CRU after the final treatment period, participants will return for further outpatient assessments (safety, PK, and immunogenicity) until 12 weeks after the final dose.

Study Schema



Abbreviations: CRU = Clinical research unit

Figure 1: Illustration of Study Design for Protocol I5T-MC-AACP

6. BLINDING

This is a non-randomized, open-label study.

7. TREATMENT

The following shows the study treatment abbreviation that will be used in the TFLs.

Study Treatment Name	Treatment order in TFL
350 mg donanemab Q2W	1

Abbreviations: Q2W = every 2 weeks

8. SAMPLE SIZE JUSTIFICATION

Approximately 40 participants may be enrolled so that approximately 25 participants complete the study. The sample sizes described are customary for Phase 1 studies evaluating safety, PK, and immunogenicity and is not powered on the basis of statistical hypothesis testing.

9. DEFINITION OF ANALYSIS POPULATIONS

The "Entered" population will consist of all participants who sign the informed consent form.

The "Enrolled" population will consist of all enrolled participants.

The "Safety" population will consist of all participants randomly assigned to study intervention and who take at least 1 dose of study donanemab. Participants will be analyzed according to the amount of intervention they actually received.

The "Pharmacokinetic" population will consist of all enrolled participants who received at least 1 full dose of donanemab and have baseline and at least one post-baseline evaluable PK sample. Participants will be analyzed according to the amount of intervention they actually received.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants are assigned to analysis populations.

10. STATISTICAL METHODOLOGY

10.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum, maximum and number of observations; for log-normal data (e.g. the PK parameters: area under the concentration versus time curve [AUCs] and maximum observed drug concentration [C_{max}]) the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

For change from baseline summary statistics, each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at that time point. The individual participants' change from baseline values will be used to calculate the summary statistics (arithmetic mean, arithmetic SD, median, minimum, maximum and number of observations) using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

10.2 Demographics and Participant Disposition

Participant disposition will be summarized and listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized and listed. All other demographic variables will be listed only.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

Noncompartmental methods applied with a validated software program (WinNonlin Phoenix v8.3.5 or higher) to the serum concentrations of LY3002813 (donanemab), will be used to determine the following PK parameters, when possible:

Serum Pharmacokinetic Parameters of LY3002813 (Donanemab):

Parameter	Units	Definition
$AUC_{0\text{-}4weeks}$	ug*h/mL	area under the concentration versus time curve from time 0 to 4weeks (Month 1, 2 and 3)[a]
$AUC_{0\text{-}2weeks}$	ug*h/mL	area under the concentration versus time curve for first dosing interval (Treatment Period 1 to 6)
$AUC_{\tau,ss}$	ug*h/mL	area under the concentration versus time curve during one dosing interval at steady state (Treatment Period 6)
$AUC(0\text{-}t_{last})$	ug*h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration (Treatment Periods 1 to 6)
$AUC\ (0\text{-}\infty)$	ug*h/mL	area under the concentration versus time curve from zero to infinity (only after 1st dose and after last dose on Day 71)
$\%AUC(t_{last}\text{-}\infty)$		Percentage of $AUC(0\text{-}\infty)$ extrapolated
$C_{max,ss}$	ug/mL	maximum observed drug concentration during a dosing interval at steady state (Treatment Period 6)
C_{max}	ug/mL	maximum observed drug concentration (Treatment Periods 1 to 5)
C_{min}	ug/mL	minimum observed drug concentration during a dosing interval at steady state (Treatment Period 1 to 5)
$C_{min,ss}$	ug/mL	minimum observed drug concentration during a dosing interval at steady state (Treatment Period 6)
$t_{1/2}$	days	half-life associated with the terminal rate constant (λz) in non-compartmental analysis (Treatment Period 6)
t_{max}	days	time to maximum observed drug concentration (Treatment Period 1 to 5)
$t_{max,ss}$	days	time to maximum observed drug concentration at steady state (Treatment Period 6)
$CL_{,ss}$	L/h	total body clearance of drug calculated at steady state after intravenous administration (Treatment Period 6)

V_{ss}	L	volume of distribution at steady state following intravenous administration (Treatment Period 6)
RA_{AUC}		accumulation ratio for $AUC_{\tau,ss}$ at steady state / $AUC_{0\text{-}2weeks}$[b]
RA_{Cmax}		accumulation ratio for $C_{max,ss}$ at steady state / $C_{max,\ day\ 1}$[b]

[a] Parameter will be calculated as the sum of $AUC_{0\text{-}2weeks}$ for treatment periods 1 and 2 (Month 1), periods 3 and 4 (Month 2) and periods 5 and 6 (Month 3).
[b] $AUC_{\tau,ss}$ and $C_{max,ss}$ based on Period 6; $AUC_{0\text{-}2weeks}$ and C_{max} values based on Period 1

Additional PK parameters may be calculated, as appropriate.

The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final CSR. Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times which will be set to zero. For non-bolus, multiple dose profiles, the pre-dose time will be set to zero unless a time deviation falls outside of the protocol blood collection time window which is considered to impact PK parameter derivation.

- C_{max} will be reported from observed values.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification, with at least one of these concentrations following C_{max}. AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{1/2}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{1/2}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{1/2}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on predicted C_{last} will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK Parameters with the exception of special handling of certain concentrations reported below the lower limit of quantitation (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:

    - The compound is non-endogenous.

    - The samples are from the initial dose period for a participant or from a subsequent dose period following a suitable wash-out period.

    - The time points occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.

- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

For multiple-dosing data, when pre-dose concentrations are missing, the value to be substituted will be C_{min} for the dosing interval.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.
- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.

- The average concentration profiles will be graphed using arithmetic average concentrations.

- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.

- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.

- Concentrations excluded from the mean calculation will be documented in the final study report.

- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.

- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If n≥6, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

    a. Transform all values in the calculation to the logarithmic domain.

    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.

    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 1 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final CSR. Approval of the final CSR will connote approval of the exclusion.

10.3.2 Pharmacokinetic Statistical Methodology

No formal statistical analysis is planned for this study. The PK parameters will be listed and summarized by study week using standard descriptive statistics. Insert stats methodology here.

10.4 Safety and Tolerability Assessments

10.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (AE) will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as a condition that starts before the participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A TEAE is defined as an AE which occurs post-dose or which is present prior to dosing and becomes more severe post-dose.

All AEs will be listed. TEAEs will be summarized by severity and relationship to the study drug. The frequency (the number of AEs, the number of participants experiencing an AE and the percentage of participants experiencing an AE) of treatment-emergent AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) (version is documented in the Data Management Plan [DMP]) system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug by the investigator. Any SAEs and product complaints will be listed. AEs by week of onset will be presented.

Discontinuations due to AEs will be listed.

10.4.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization drug dictionary (version is documented in the DMP). Concomitant medication will be listed.

10.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by time point, and listed. Urinalysis data will be listed. Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual participant data listings.

10.4.4 Vital signs

Vital signs data collected during the treatment periods will be summarized by time point together with changes from baseline, where baseline is defined as the Day 1 pre-dose assessment in each treatment period. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

Values for individual participants will be listed.

10.4.5 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes only and will not be presented. Any clinically significant findings from ECGs will be reported as an AE.

10.4.6 Hepatic Monitoring

If a participant experiences elevated laboratory parameters, as detailed in Section 8.2.8.1 of the protocol, additional tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

The participants' liver disease history and associated person liver disease history data will be listed. Use of acetaminophen during the study, which has potential for hepatotoxicity, will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography scan, and biopsy assessments will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized and listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual participant data listings.

10.4.7 Immunogenicity Assessments

Immunogenicity data will be listed and frequency tables will be presented if analysed. The frequency and percentage of participants with pre-existing ADA and with TE ADAs will be presented. TE ADAs are those that are boosted or induced by exposure to study drug, with a 4-fold increase in titer compared to baseline if ADAs were detected at baseline or a titer 2-fold greater than the minimum required dilution (1:5 if no ADAs were detected at baseline, where baseline is defined as sample taken on Day -1 in Treatment Period 1.

The frequency and percentage of participants with neutralizing antibodies, if measured, may also be tabulated for participants with TE ADA.

To assess the relationship between the PK parameters and ADA, a box plot of $CL_{,ss}$ versus TE ADA status (TE ADA+ versus TE ADA-) will be presented. Scatter plots will be presented for the observed C_{trough} (y - axis) vs ADA titer (Day 15, 29, 43, 57, 71) also boxplot of individual CLss vs ADA titer. Additional analyses may be conducted, if appropriate.

10.4.8 Neurological Examinations

The below table presents the scoring of the neurological examination findings.

Score	0	1	2	3	4
Tremor	Absent	Visible with limb extension and/or careful inspection	Visible without limb extension	Interferes with motor function	
Nystagmus	Absent	1 to 3 beats on lateral gaze	>3 beats on lateral gaze	Present on forward gaze	
Reflexes (brachial or patellar)	Normal	Trace	Absent	Increased	Clonic
Finger-nose	Normal	Abnormal			
Romberg sign	Absent	Present			

The frequency of neurological survey data will be summarized by time point, and listed. For tremor, nystagmus and reflexes, only data from the nonspecific location assessment will be summarized. The overall neurological assessment will also be summarized by timepoint.

10.4.9 Columbia Suicide Severity Rating Scale (C-SSRS)

Data from the C-SSRS questionnaire will be listed.

10.4.10 Hypersensitivity reactions

For all drug hypersensitivity and anaphylactic reactions, additional follow-up data will be collected to assess the participant's medical history, alternative causes, and symptoms. The relationship between hypersensitivity reactions and TE-ADAs as well as PK parameters may be explored.

These data will be listed.

10.4.11 Infusion Related Reactions

Infusion related reactions data will be summarized and listed. The relationship between IRRs and TE-ADAs as well as PK parameters may be explored.

10.4.12 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

10.4.13 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11. INTERIM ANALYSES

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

Access to safety, PK, and immunogenicity data may occur on an ongoing basis throughout the study. The purpose of these reviews is to inform the design of subsequent studies.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

14. DATA PRESENTATION

14.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. Number of observations and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

14.2 Missing Data

Missing data will not be displayed in listings.

14.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of participants or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

Approved on 01 Mar 2023 GMT

15. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.
Final Version 2.0	28FEB2023	1) Updated number of subjects in study design and sample size section as per protocol amendment 2) 10.3.1 Updated the PK Parameters definition 3) Enrolled population definition included for more clarity in TFL's

NA = not applicable

Signature Page for VV-CLIN-082328 v1.0

Approval	PPD Statistician 28-Feb-2023 16:45:54 GMT+0000

Approval	PPD Project Leader 28-Feb-2023 17:00:30 GMT+0000

Approval	PPD Statistician 28-Feb-2023 17:03:57 GMT+0000

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