AACK Statistical Analysis Plan v1.0

A Parallel-group Treatment, Phase 1, Participant- and Investigator-Blind, Randomized, 3 Arm Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Intravenous Dose of Donanemab Compared with Placebo in Healthy Chinese Participants

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STATISTICAL ANALYSIS PLAN

A Parallel-group Treatment, Phase 1, Participant- and Investigator-Blind, Randomized, 3 Arm Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Intravenous Dose of Donanemab Compared with Placebo in Healthy Chinese Participants

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Clinical Phase I

1. TABLE OF CONTENTS

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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}-∞)	Percentage of AUC(0-∞) extrapolated
AE	Adverse event
ADA	Anti-drug antibody
AUC	Area under the concentration versus time curve
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 lower limit of quantitation
C_{last}	Last quantifiable drug concentration
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SD	Standard deviation
SOP	Standard Operating Procedure
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

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V_{ss}	Volume of distribution at steady state following intravenous administration
V_z	Volume of distribution during the terminal phase after intravenous administration

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 11 Jan 2022) and protocol amendment (a) dated 17 Jun 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 unblinding. 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 investigate the safety and tolerability of donanemab versus placebo following single dose intravenous (IV) administration in healthy Chinese participants	• Incidence of treatment-emergent adverse events (TEAE), serious adverse events (SAE)
Secondary	
• To characterize the pharmacokinetic profile of donanemab following single dose IV administration in healthy Chinese participants	• Maximum observed drug concentration (C_{max}) and area under the concentration versus time curve from time zero to infinity ($AUC_{0-\infty}$)
Exploratory	
• To characterize immunogenicity of donanemab following single dose IV administration in healthy chinese participants	• Incidence of treatment-emergent anti-drug antibodies (TE-ADA)

5. STUDY DESIGN

This is a parallel treatment, Phase 1, participant- and investigator-blind, placebo-controlled, randomized study to evaluate the safety, tolerability, and PK of a single IV dose of donanemab in healthy Chinese participants. This study will be conducted in China. Up to 36 participants may be enrolled so that approximately 30 participants complete the study.

The study will include 3 cohorts, each with 12 participants randomized in a 5 (donanemab): 1 (placebo) ratio.

The planned doses are:

- Cohort 1: 350 mg IV single dose
- Cohort 2: 700 mg IV single dose
- Cohort 3: 1400 mg IV single dose

Screening Period

Screening may occur up to 28 days prior to randomization and dosing with study intervention. 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. In such instances, the following screening tests and procedures may be repeated: vital signs and clinical laboratory tests.

Inpatient Period

Eligible participants will be admitted to the clinical research unit (CRU) on Day -1 prior to dosing with study intervention. On Day 1, participants will be dosed with a single IV dose of donanemab or placebo. Participant will be discharged on Day 5 at the discretion of the investigator and after completion of all assessments. Participants will be monitored for safety and PK, and immunogenicity samples will be collected.

Follow-up Period

After discharge from the CRU, participants will be required to visit the CRU on an outpatient basis. The follow-up period will be 12 weeks ± 7 days after completion of dosing or until early discontinuation.

6. BLINDING

This is a randomized participant- and investigator-blind study. All measures possible must be taken to maintain the blind; access to the blinding information will be restricted to authorized personnel as described in the protocol. All study site personnel, except staff who prepare the study intervention, will be blinded to treatment allocation.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. In such cases, the unblinding is to be conducted according to the protocol.

The Labcorp biometrics and Eli Lilly study teams will be unblinded throughout the study.

7. TREATMENTS

The following is a list of the study treatment abbreviations that will be used in the TFLs.

Cohort	Study Treatment Name	Treatment order in TFL
1 to 3	Placebo IV	1
1	350 mg Donanemab IV	2
2	700 mg Donanemab IV	3
3	1400 mg Donanemab IV	4

Abbreviations: IV = intravenous

8. SAMPLE SIZE JUSTIFICATION

Approximately 36 participants may be enrolled in 3 dosing cohorts. The sample sizes described are customary for Phase 1 studies evaluating safety and PK parameters and is not powered on the basis of statistical hypothesis testing. Each cohort will comprise approximately 12 participants with a randomization ratio of 5:1 between donanemab and placebo. Participants who discontinue the study before completing may be replaced at the discretion of the sponsor and investigator. The replacement participant can complete the entire study period.

9. DEFINITION OF ANALYSIS POPULATIONS

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

The "Safety" population will consist of all participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the 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 1 postbaseline evaluable PK sample. Participants will be analyzed according to the 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 n; for log-normal data (e.g. the PK parameters: area under the concentration versus time curve [AUC] and 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 timepoint. The individual participant's 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 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 (Phoenix WinNonlin Version 8.1.1 or later) to the serum concentrations of donanemab will be used to determine the following PK parameters, when possible:

Parameter	Units[a]	Definition
AUC(0-t_{last})	h*ng/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
AUC(0-∞)	h*ng/mL	area under the concentration versus time curve from time zero to infinity[b]
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{½}$	h	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
CL	L/h	total body clearance of drug calculated after intravenous administration
V_z	L	volume of distribution during the terminal phase after intravenous administration
V_{SS}	L	volume of distribution at steady state following intravenous administration

[a]Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b]Based on the last observed quantifiable concentration

Additional PK parameters may be calculated, as appropriate.

Exploratory graphical analyses relating donanemab serum exposure and immunogenicity may be conducted.

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.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.

- 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 3 consecutive serum concentrations above the lower limit of quantitation, with at least 1 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 ($t_{½}$) 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 serum 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 $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ 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 last quantifiable drug concentration (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). Serum 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 2 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.

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 CSR.
- 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 CSR.

Treatment of Outliers during PK 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.

<u>Data within an Individual Profile</u>

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

- 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 the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.

2. 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 ≥ 6 following the exclusion, then repeat step 2 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 of donanemab will be listed and summarized by treatment using standard descriptive statistics.

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 postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. TEAEs will be summarized by treatment, 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 TEAEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 (or later) 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 serious AEs will be listed.

Discontinuations due to AEs will be listed.

10.4.2 Concomitant medication

Concomitant medication will be coded using the world health organization (WHO) drug dictionary (Version B3 March 2022). Concomitant medication will be listed.

10.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter and treatment together with changes from baseline, where baseline is defined as the Day -1 predose assessment, 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 will be summarized by treatment and timepoint together with changes from baseline, where baseline is defined as the Day 1 predose assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by parameter and 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

Hepatic monitoring will be performed as outlined in Section 8.2.6.2. of 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 by treatment 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 antidrug antibody (ADA) and with TE-ADAs will be presented by treatment. TE-ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA), where baseline is defined as Day 1 predose.

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

10.4.8 Hypersensitivity reactions

For all drug hypersensitivity reactions that occur, additional follow-up data will be collected to assess the patient's medical history, alternative causes, and symptoms.

These data will be listed.

10.4.9 Neurological Examination

A directed neurological examination will be performed by the investigator at the time points specified in the protocol. If clinically significant abnormalities are noted at these time points, additional examinations should be performed as clinically necessary. The examiner should be familiar with the participant's baseline examination. Elements of the examination may include inspection for tremor, extraocular movements, brachial and patellar deep tendon reflexes, finger-nose pointing, and Romberg sign.

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 treatment and timepoint, and listed.

10.4.10 Infusion-Related Reactions

Infusion-related reaction data will be listed and summarized by treatment in frequency tables.

10.4.11 Pharmacogenetic Samples

Pharmacogenetic data for apolipoprotein E genotype ε4 carrier status will be listed.

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 statistical analyses are planned.

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.”

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.

NA = not applicable

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