Statistical Analysis Plan (V2): J2Z-MC-PGAA

A Phase 1, Randomized, Placebo-Controlled Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Immunogenicity of LY3832479 Given as a Single Intravenous Dose in Healthy Participants

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STATISTICAL ANALYSIS PLAN

A Phase 1, Randomized, Placebo-Controlled Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Immunogenicity of LY3832479 Given as a Single Intravenous Dose in Healthy Participants

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Clinical Phase I

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1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
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
%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
BQL	Below the lower limit of quantification
CL	Total body clearance of drug calculated
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
DAIDS	Division of Allergy and Infectious Diseases
ECG	Electrocardiogram
ICF	Informed consent form
ICH	International Conference on Harmonisation
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
TFLs	Tables, Figures, and Listings

$t_{½}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TBL	Total bilirubin
t_{last}	Time of the last observed drug concentration
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
V_z	Volume of distribution during the terminal phase
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 03 June 2020) and Protocol Amendment (c) (final version dated 15 July 2020).

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. 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

4.1 Primary Objective

To investigate the safety and tolerability of a single dose of LY3832479 in healthy participants.

The primary endpoints are serious and non-serious adverse events (AE), laboratory measures of safety, electrocardiogram (ECG), and vital signs.

4.2 Secondary Objective

To characterize the PK of LY3832479 following a single intravenous (IV) administration of LY3832479 to healthy participants.

The secondary endpoints are area under the concentration versus time curve (AUC) and maximum observed drug concentration (C_{max}).

5. STUDY DESIGN

Study PGAA is a Phase 1, randomized, placebo-controlled study of LY3832479 administered to healthy participants. A study schema for PGAA can be seen in Figure 1.

The study will comprise up to 3 cohorts:

Cohorts 1 and 2 (at least 9 participants):

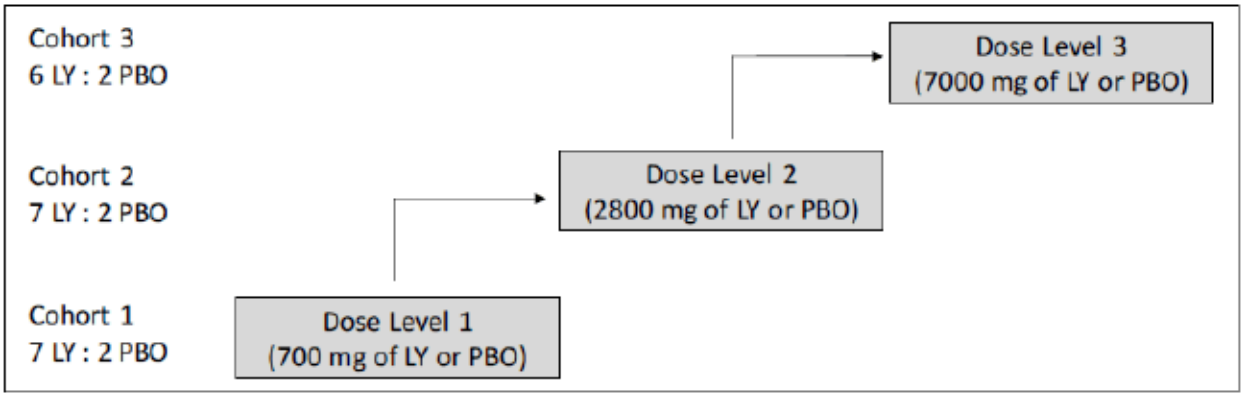
- 7 randomized to LY3832479 and
- 2 randomized to placebo.

Cohort 3 (at least 8 participants):

- 6 randomized to LY3832479 and
- 2 randomized to placebo.

A maximum of 30 participants will be enrolled to study intervention such that approximately 8 participants have sufficient evaluable data in each cohort.

After at least 7 participants have completed Day 4 in a given cohort, all safety data up to this cutoff date will be reviewed to determine whether the next cohort can be dosed, as well as the dose to be used, after agreement between the Lilly's medical monitor and the investigator. Safety and tolerability data will be the primary criteria guiding dose-escalation.



Abbreviations: LY = LY3832479; PBO = placebo.

Figure 1: A general schema for study J2Z-MC-PGAA

6. 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
All	Pooled placebo IV	1
1	700 mg LY3832479 IV	2
2	2800 mg LY3832479 IV	3
3	7000 mg LY3832479 IV	4

7. SAMPLE SIZE JUSTIFICATION

A maximum of 30 participants will be enrolled to study intervention such that approximately 8 participants have sufficient evaluable data in each cohort.

The sample size not powered on the basis of statistical hypothesis testing. However, the number of subjects is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the trial.

8. DEFINITION OF ANALYSIS POPULATIONS

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

The "Safety" population will consist of all participants randomly assigned to study intervention (LY3832479 or placebo) and who are administered at least 1 dose of study intervention.

The "Pharmacokinetic" population will consist of all randomized participants who received study intervention (LY3832479), have baseline, and have multiple evaluable PK samples.

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

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that are 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: AUCs 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 subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

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

9.2 Demographics and Subject Disposition

Subject disposition will be summarized and listed. The demographic variables age, sex, race, ethnicity, body weight, height and body mass index will be summarized and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

Venous blood samples will be collected as specified in the protocol's schedule of assessments for determination of concentrations of serum LY3832479 used to evaluate the PK of LY3832479.

9.3.1 Pharmacokinetic analysis

Any PK analyses prior to database lock will be the responsibility of Eli Lilly PK/PD group, whereas any PK analyses post database lock will be reported by Covance.

Noncompartmental methods applied with a validated software program (Phoenix WinNonlin Version 8.1 or later) to the serum concentrations of LY3832479 will be used to determine the following PK parameters, when possible:

Parameter	Units[a]	Definition
$AUC(0\text{-}t_{last})$	µg.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
$AUC(0\text{-}\infty)$	µg.h/mL	Area under the concentration versus time curve from time zero to infinity
$\%AUC(t_{last}\text{-}\infty)$	%	Percentage of $AUC(0\text{-}\infty)$ extrapolated
C_{max}	µg/mL	Maximum observed drug concentration
t_{last}	h	Time of the last observed drug concentration
t_{max}	h	Time of maximum observed drug concentration
$t_{½}$	h	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL	L/h	Total body clearance of drug calculated
V_z	L	Volume of distribution during the terminal phase
V_{ss}	L	Volume of distribution at steady state

[a] Serum LY3832479 drug concentration units will come in from the bioanalytical lab as ng/mL to one decimal place; the data will be transformed to µg/mL for analysis.

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 study report.

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 time of maximum observed drug concentration (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 three consecutive serum 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 ($t_{½}$) 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 subject 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 will be reported (except in bioequivalence and bioavailability studies, where only the observed parameters 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 quantification (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 subject 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.

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 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 $n\geq6$, 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 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 report. Approval of the final report will connote approval of the exclusion.

9.3.2 Pharmacokinetic statistical methodology

All PK parameters will be summarized by treatment using descriptive statistics.

The PK parameter estimates will be evaluated to delineate dose proportionality. Log-transformed C_{max}, and AUC(0-∞) of LY3832479 will be evaluated using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means and corresponding 90% confidence intervals. In addition, results of the dose proportionality will be plotted.

The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality.

Example SAS code for the analysis:

```
proc mixed data=pk;
   model log_pk = log_dose / alpha=0.1 cl solution residual ddfm=kr;
   estimate '700 mg'  intercept 1 log_dose 2.87506126 / alpha=0.1 cl; /*Log of 700 */
   estimate '2800 mg' intercept 1 log_dose 3.44715803 / alpha=0.1 cl; /*Log of 2800 */
   estimate '7000 mg' intercept 1 log_dose 3.84509804 / alpha=0.1 cl; /*Log of 7000 */
   estimate '2800 mg - 250 mg'    log_dose 0.97003679 / alpha=0.1 cl; /*Difference in
   log values of 7000 and 700 */
   ods output solutionf=est;
   ods output estimates=estims;
run;
```

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the 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 an AE that starts before the subject 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 treatment-emergent AE 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. Treatment-emergent AEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 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. Onset times will be calculated from the start of the infusion.

Discontinuations due to AEs will be listed.

9.4.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version WHODD MAR20B3). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter and treatment together with changes from baseline, and listed. Baseline is defined as the Day 1 predose assessment. Additionally, clinical chemistry and hematology data outside the reference ranges will be listed and flagged on individual subject data listings.

9.4.4 Vital signs

Vital signs data will be summarized by treatment 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 treatment.

Values for individual subjects will be listed.

9.4.5 Electrocardiogram

All 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.

9.4.6 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq$3× upper limit of normal (ULN), alkaline phosphatase (ALP) $\geq$2× ULN, or elevated total bilirubin (TBL) $\geq$2× ULN, liver 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 subjects' liver disease history and associated person liver disease history data will be listed. Any concomitant medications that have potential for hepatotoxicity, including acetaminophen will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) 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 subject data listings.

9.4.7 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.

9.4.8 Infusion-site reactions

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

The severity of all ISRs will be assessed using the Division of Allergy and Infectious Diseases (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

9.4.9 Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection

Data from SARS-CoV-2 clinical screening, serology, and point-of-care test will be listed, if available.

9.4.10 Other assessments

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

9.4.11 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim statistical analyses are planned.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. 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.

13. DATA PRESENTATION

13.1 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. N 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.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects 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.".

14. VERSION HISTORY

The SAP Version 2 was created to capture changes introduced by the three protocol amendments that were published since finalization of SAP Version 1. These changes mainly affected Section 5 of the SAP. Additionally, minor wording change was applied so that the Safety analysis population matches the wording of the protocol in Section 8.

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