Statistical Analysis Plan I8D-MC-AZEP

An Absolute Bioavailability Study of LY3314814 in Healthy Subjects Using an Intravenous Tracer Method

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STATISTICAL ANALYSIS PLAN

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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
ANOVA	Analysis of variance
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
CL	Total body clearance of drug calculated after IV administration
C_{last}	Last quantifiable drug concentration
CL/F	Apparent total body clearance of drug calculated after extra vascular administration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
DN	Dose normalised
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
ICH	International Council on Harmonisation
IV	Intravenous
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SD	Standard deviation

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
WHO	World Health Organization
V_{ss}	Volume of distribution at steady state after IV administration
V_{ss}/F	Apparent volume of distribution at steady state after extra-vascular administration
V_z	Volume of distribution during the terminal phase after IV administration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 07 November 2016), Protocol Amendment (a) (final version dated 07 June 2017), Protocol Amendment (b) (final version dated 21 August 2017), Protocol Amendment (c) (final version dated 06 September 2017), and Protocol Amendment (d) (final version dated 13 October 2017).

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 between Eli Lilly and Company and PPD . 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 signed off prior to first subject administration for this study. 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 between Eli Lilly and Company and PPD 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 Council 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

The primary objective is to estimate the absolute bioavailability of LY3314814 following simultaneous administration of a single oral dose of 50 mg LY3314814 and a 2- hour intravenous (IV) infusion of approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814(+)- Camsylate (referred to as [$^{13}C_4{}^{15}N_3$]-LY3314814 from this point forward) in healthy subjects.

4.2 Secondary Objectives

The secondary objectives are:

- To assess the safety of LY3314814 following simultaneous administration of a single oral dose of 50 mg LY3314814 and a 2-hour IV infusion of approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814 in healthy subjects.

- To characterize the PK parameters of LY3314814 and [$^{13}C_4{}^{15}N_3$]-LY3314814 following simultaneous administration of a single oral dose of 50 mg LY3314814 and a 2-hour IV infusion of approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814 in healthy subjects.

5. STUDY DESIGN

This is a Phase 1, single-center, open-label, single-period study to estimate the absolute bioavailability of LY3314814 in healthy male and female subjects not of childbearing potential.

Subjects will be admitted to the clinical research unit (CRU) on Day -1 and will remain resident in the CRU for at least 48 hours after the start of infusion, followed by outpatient visits on Days 4, 5 and 6. A follow-up visit will occur at least 7 days postdose. On Day 1, following an overnight fast of at least 8 hours, subjects will receive a single oral dose of 50 mg LY3314814 and at approximately the same time an IV infusion of approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814 will be started. The infusion will run for 2 hours. Blood samples will be collected predose and up to 120 hours postdose to measure LY3314814 and [$^{13}C_4{}^{15}N_3$]-LY3314814 concentrations.

6. TREATMENT

The following label for study treatment will be used in the TFLs: 50 mg LY3314814 oral + 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814 IV. PK data will summarised separately for each administration.

7. SAMPLE SIZE JUSTIFICATION

Up to 8 subjects may be enrolled and dosed to ensure that at least 6 subjects complete and have evaluable PK data.

This sample size is considered adequate for Phase 1 studies evaluating absolute bioavailability and is not intended to meet any a priori statistical requirement.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled subjects, whether or not they completed all protocol requirements.

The "Pharmacokinetic" population will consist of all subjects who received at least one dose of study drug and have evaluable PK data. Subjects may be excluded from the PK summary statistics and statistical analysis if a subject has an adverse event (AE) of vomiting that occurs at or before 2 times median of the time of maximum observed drug concentration (t_{max}).

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 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, min, max and N; for log-normal data (e.g. the PK parameters: Area under the concentration versus time curve [AUC] and the 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 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 listed. The demographic variables age, sex, race, ethnicity, body weight, height and body mass index will be summarized and listed. All other demographics will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 6.4.1 or later).

Plasma concentrations of LY3314814 and [$^{13}C_4$ $^{15}N_3$]-LY3314814 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	ng.h/mL and ng equiv•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-∞)	ng.h/mL and ng equiv•h/mL	area under the concentration versus time curve from time zero to infinity
DN AUC(0-t_{last})	ng.h/mL/mg and ng equiv•h/mL/mg	dose normalised AUC(0-t_{last})
DN AUC(0-∞)	ng.h/mL/mg and ng equiv•h/mL/mg	dose normalised AUC(0-∞)
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	ng/mL and ng equiv/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration (LY3314814 only)
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (LY3314814 only)
V_{SS}/F	L	apparent volume of distribution at steady state after extra-vascular administration (LY3314814 only)
CL	L/h	total body clearance of drug calculated after IV administration ([$^{13}C_4$ $^{15}N_3$]-LY3314814 only)
V_Z	L	volume of distribution during the terminal phase after IV administration ([$^{13}C_4$ $^{15}N_3$]-LY3314814 only)
V_{SS}	L	volume of distribution at steady state after IV administration ([$^{13}C_4$ $^{15}N_3$]-LY3314814 only)

Dose normalised (DN) PK parameters DN AUC(0-t_{last}) and DN AUC(0-∞) will be calculated by dividing the PK parameter value by dose in mg.

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the clinical study report. 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 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 plasma concentrations above the lower limit of quantification (LLOQ), 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 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 $t_{½}$ 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 the observed 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). 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 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.

<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 $n \geq 6$ 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

To quantify the absolute bioavailability of LY3314814, a mixed-effect analysis of variance (ANOVA) model will be applied to the log-transformed DN AUC(0-∞) of LY3314814 obtained after oral dosing and that of the IV administered [$^{13}C_4{}^{15}N_3$]-LY3314814. The model will contain formulation (oral or IV) as a fixed effect and subject as a random effect. The absolute bioavailability will be expressed as the ratio of the least-squares geometric means of the formulations (oral:IV) along with its corresponding 90% confidence interval.

Example SAS code:

```
proc mixed data=DATA alpha=0.1;
   class treatment subject;
   model log_pk = treatment / ddfm=kr;
   random subject;
   lsmeans treatment / pdiff cl alpha=0.1;
   ods output lsmeans=lsmeans;
   ods output diffs=diffs;
run;
```

Additional analysis may be conducted if deemed appropriate.

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 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 Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 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. Any serious AEs will be tabulated. Onset time of AEs will derived relative to the oral administration.

9.4.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version March 2017). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry, hematology and urinalysis data will be listed. Additionally clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed.

Values for any clinical chemistry, hematology and urinalysis values outside the reference ranges will be flagged on the 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 Day 1 predose.

Furthermore, values for individual subjects will be listed.

9.4.5 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes only and will not be presented.

9.4.6 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥2× ULN, liver tests will be performed to confirm the abnormality.

The subjects' liver disease history and associated person liver disease history data will be listed. Any concomitant medication of acetaminophen/paracetamol will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and a biopsy assessment 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 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analysed. Prior therapy data will be listed.

9.4.8 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 centre of the table, such as, "No serious adverse events occurred for this study."