Statistical Analysis Plan: I8K-MC-JPDF (Final)

Relative Bioavailability and the Effect of Food on the Bioavailability of LY3337641 in Healthy Subjects

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STATISTICAL ANALYSIS PLAN

Relative Bioavailability and the Effect of Food on the Bioavailability of LY3337641 in Healthy Subjects

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2. ABBREVIATIONS

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

AE	Adverse event
API	Active pharmaceutical ingredient
AUC	Area under the concentration versus time curve
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(0-∞)	Area under the concentration versus time curve from zero to infinity
%AUC(tlast-∞)	Percentage of AUC(0-∞) extrapolated
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
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
ICH	International Conference on Harmonisation
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PSD	Particle size distribution
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
V_{ss}/F	Apparent volume of distribution at steady state after extra-vascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 09 January 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 CCI . 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 CCI 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 evaluate the relative bioavailability of a single 20 mg dose of LY3337641 as the commercial image tablet (esylate salt) [$T1_{fasted}$] compared to the Phase 1/2 tablet (diHCl salt) [R_{fasted}].

4.2 Secondary Objectives

- To evaluate the effect of a high-fat meal on the bioavailability of a single 20 mg dose of LY3337641 when administered as the commercial image tablet (esylate salt) [$T1_{fed}$].

- To evaluate the relative bioavailability of a single 20 mg dose of LY3337641 when administered as the large active pharmaceutical ingredient (API) particle size distribution (PSD) commercial image tablet (esylate salt) [$T2_{fasted}$] compared to the commercial image tablet (esylate salt) [$T1_{fasted}$].

- To assess the tolerability of LY3337641 when administered as a single 20 mg dose to healthy subjects.

5. STUDY DESIGN

This is an open-label, 4-period, 4-sequence, randomized, crossover study in healthy subjects. Up to 32 subjects may be enrolled in order to ensure that at least 24 subjects complete the study (ie, complete all 4 treatment periods).

Subjects will receive single oral doses of 20 mg LY3337641 on 4 separate occasions. Each subject will receive the following:

- Reference formulation (R_{fasted}): 20 mg LY3337641 Phase 1/2 tablet (diHCl salt) administered in the fasted state;
- Test formulation 1 ($T1_{fasted}$): 20 mg LY3337641 commercial image tablet (esylate salt) administered in the fasted state;
- Test formulation 1 ($T1_{fed}$): 20 mg LY3337641 commercial image tablet (esylate salt) administered in the fed state;
- Test formulation 2 ($T2_{fasted}$): 20 mg LY3337641 large API PSD commercial image tablet (esylate salt) administered in the fasted state.

Subjects will be randomly allocated to one of the treatment sequences below:

Sequence	Period 1	Period 2	Period 3	Period 4
1	Reference formulation (R_{fasted})	Test formulation 2 ($T2_{fasted}$)	Test formulation 1 ($T1_{fasted}$)	Test formulation 1 ($T1_{fed}$)
2	Test formulation 1 ($T1_{fasted}$)	Reference formulation (R_{fasted})	Test formulation 1 ($T1_{fed}$)	Test formulation 2 ($T2_{fasted}$)
3	Test formulation 1 ($T1_{fed}$)	Test formulation 1 ($T1_{fasted}$)	Test formulation 2 ($T2_{fasted}$)	Reference formulation (R_{fasted})
4	Test formulation 2 ($T2_{fasted}$)	Test formulation 1 ($T1_{fed}$)	Reference formulation (R_{fasted})	Test formulation 1 ($T1_{fasted}$)

In each period, subjects will be admitted to the clinical research unit (CRU) on Day -1. In each treatment period, subjects will be fasted overnight and a single dose of 20 mg LY3337641 will be administered in the morning of Day 1. Subjects will receive a high-fat meal prior to dosing with LY3337641 if applicable. Subjects will reside at the CRU until the collection of the 72-hour PK blood sample.

There will be a washout period of at least 5 days between dose administrations in consecutive periods.

If the investigator decides not to administer the first dose to a subject or not to enroll a subject on a particular day, the subject may be rescheduled to participate in the study; and any procedures performed up to that point may be repeated.

Blood samples will be collected up to 72 hours after each dosing occasion for the measurement of plasma concentrations of LY3337641.

6. TREATMENTS

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

Study Treatment Name	Abbreviation	Treatment order in TFLs
20 mg LY3337641 Phase 1/2 tablet (diHCl salt) (Reference fasted)	R_{fasted}	1
20 mg LY3337641 commercial image tablet (esylate salt) (Test 1 fasted)	$T1_{fasted}$	2
20 mg LY3337641 commercial image tablet (esylate salt) (Test 1 fed)	$T1_{fed}$	3
20 mg LY3337641 large API PSD commercial image tablet (esylate salt) (Test 2 fasted)	$T2_{fasted}$	4

7. SAMPLE SIZE JUSTIFICATION

Up to 32 subjects may be enrolled in order to ensure that 24 subjects complete all 4 study periods.

The sample size chosen will provide a precision of 8% for the estimate of the geometric mean ratio in area under the concentration versus time curve (AUC) between the test formulations versus the reference formulation, and between the test formulations administered in the fed versus the fasted state. It means that there is a 90% probability that the half-width of the resulting 90% confidence interval (CI) of the geometric mean ratio in AUC is no larger than 8%. No direct estimate of intra-subject variability is available.

The sample size chosen will provide a precision of 13% for the estimate of the geometric mean ratio in maximum observed drug concentration (C_{max}) between the test formulations versus the reference formulation, and between the test formulations administered in the fed versus the fasted state. It means that there is a 90% probability that the half-width of the resulting 90% CI of the geometric mean ratio in C_{max} is no larger than 13%. No direct estimate of intra-subject variability is available.

Based on Study JPDD, the coefficient of variation (CV%) for AUC and C_{max} were approximately 30% and 50%, respectively, for a 20 mg dose of LY3337641 administered. Assuming that half

of the total CV% is contributed by intra-subject variability, an approximation of the intra-subject variability of 15% for AUC and 25% for C_{max}.

Subjects who are randomized but not complete all 4 treatment periods may be replaced to ensure that enough subjects complete the study. The replacement subject will assume the withdrawn subject's treatment sequence (receiving each treatment allocated).

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all subjects who received at least one dose of study drug, 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. PK data may be excluded from the summary statistics and statical analysis where a subject has an adverse event (AE) of vomiting that occurs at or before 2 times median 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: AUCs and C_{max}) the geometric mean and geometric 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 9.3 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.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Noncompartmental methods applied with a validated software program (Phoenix WinNonlin Version 6.4 or later) to the plasma concentrations of LY3337641, will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	ng•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	area under the concentration versus time curve from zero to infinity
%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
$t_{1/2}$	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
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration
V_{SS}/F	L	apparent volume of distribution at steady state after extra-vascular administration

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 predose sampling times which will be set to zero. For non-bolus, multiple dose profiles, the predose 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} 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 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). 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 predose 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 predose 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 lo g 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 report. Approval of the final report will connote approval of the exclusion.Insert from PKAP (note PKAP should detail WinNonlin version)

9.3.2 Pharmacokinetic Statistical Methodology

The PK parameter estimates for LY3337641 will be compared between formulations and between the fed and fasted states. Log-transformed AUC(0-∞), AUC(0-t_{last}) and C_{max} estimates will be analyzed using a linear mixed-effects model with fixed effects for treatment, period, and sequence and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CI.

One model will be used for all of the following comparisons:

- Relative bioavailability: test formulation 1 ($T1_{fasted}$) versus reference formulation (R_{fasted});

- Food effect: test formulation 1 administered in the fed state ($T1_{fed}$) versus test formulation 1 administered in the fasted state ($T1_{fasted}$);
- Relative bioavailability: test formulation 2 ($T2_{fasted}$) versus Test formulation 1 ($T1_{fasted}$).

Example SAS code:

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

The t_{max} will be analyzed non-parametrically. Median of differences and approximate 90% CI for the median of differences will be calculated for the fed versus fasted states and for the comparisons between the different formulations. P-values will also be calculated using the Wilcoxon signed rank test.

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 19.1 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.

9.4.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version September 2016). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter and treatment, and listed. 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

Supine vital signs data will be summarized by parameter and treatment together with changes from baseline, where baseline is defined as Day 1 predose (of each period). Figures of mean vital signs and mean changes from baseline will be presented by parameter and treatment.

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 Other assessments

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

9.4.7 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

An interim analysis is scheduled to occur after approximately 24 subjects complete the first 3 periods to support an internal formulation decision for clinical planning activities associated with LY3337641. The primary purpose of this interim analysis is to compare the AUC(0-∞) and C_{max} of $T1_{fasted}$ and R_{fasted}, however all available PK data will be evaluated during the interim. After Period 3, crossover data from approximately 12 subjects for these 2 treatments should be available.

A sample size of 12 subjects will provide a precision of 13% and 20% for the estimate of the geometric mean ratio in AUC and C_{max}, respectively, between the two formulations. Assumptions are the same as detailed in Section 7.

An additional interim analysis after Period 4 and before the final database lock may be conducted if needed.

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.”

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