Statistical Analysis Plan I8K-JE-JPDB

A Single- and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3337641 in Japanese and Caucasian Healthy Subjects

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STATISTICAL ANALYSIS PLAN

A Single- and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3337641 in Japanese and Caucasian Healthy Subjects

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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
AUC	Area under the concentration versus time curve
BID	Twice daily
BTK	Bruton's tyrosine kinase
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
e.g.	For example (Latin: *exempli gratia*)
EC	Early Clinical
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
IP	Investigational product
MD	Multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetic
QD	Once daily
QTcB	Bazett-corrected QT interval
QTcF	Fridericia-corrected QT interval
SAP	Statistical Analysis Plan
SD	Single dose
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 24 December 2016).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) 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 Covance Early Clinical (EC) Biometrics. 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 Covance EC Biometrics 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 explore the safety and tolerability of LY3337641 in healthy Japanese and Caucasian subjects.

4.2 Secondary Objective

- To estimate the PK parameters of single and multiple doses of LY3337641 following oral administration in healthy Japanese and Caucasian subjects.

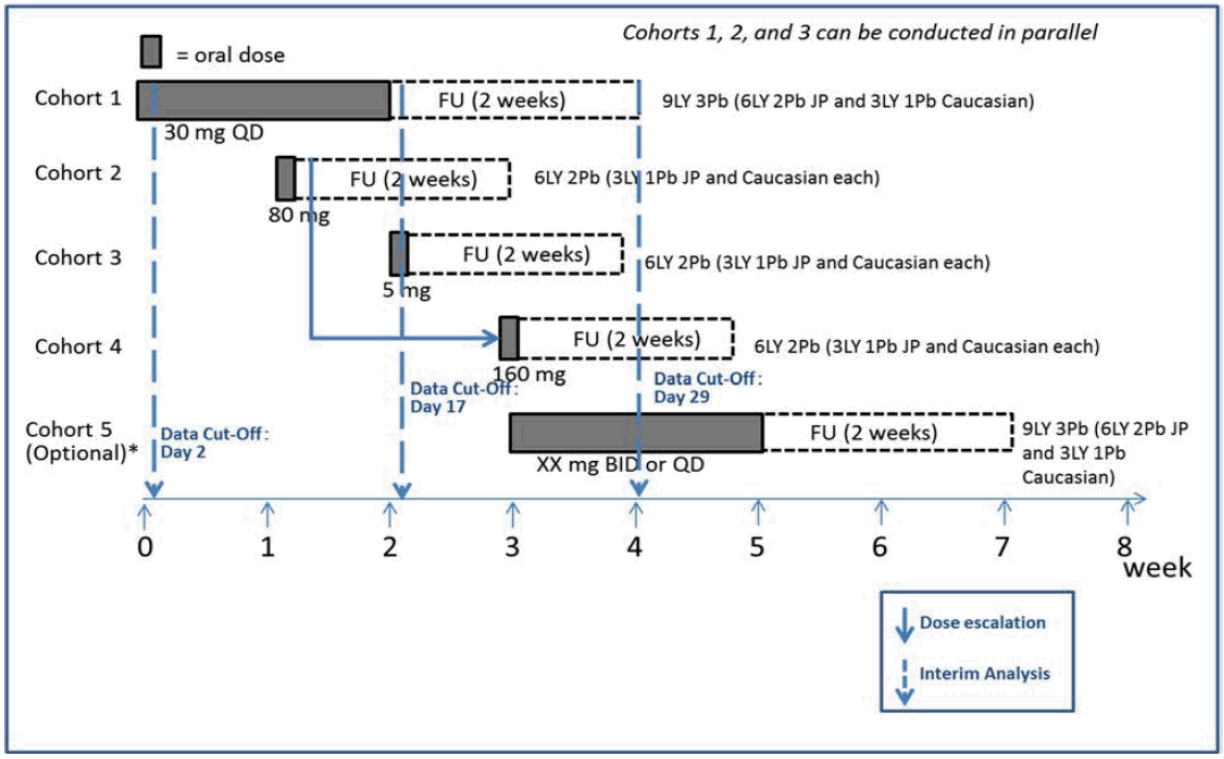
4.3 Exploratory Objectives

- To explore the PD following single and multiple doses of LY3337641 in healthy Japanese and Caucasian subjects.

- To explore the safety, tolerability, PK, and PD of LY3337641 in Japanese subjects in relation to Caucasian subjects.
- To explore the effect of LY3337641 on ECG findings in healthy Japanese and Caucasian subjects.

5. STUDY DESIGN

This is a single-site, subject- and investigator-blind, randomized, placebo-controlled, single dose (SD) and multiple dose (MD) study to assess the safety, tolerability, PK, and PD of LY3337641 in healthy Japanese and Caucasian subjects. Subjects will be randomized to LY3337641 within each cohort as shown in Figure JPDB.1. All cohorts will be randomized in a 3:1 ratio of LY3337641 to placebo. MD Cohort 1 (30 mg once daily [QD] for 2 weeks) and Cohort 5 (optional) will consist of 12 subjects (8 Japanese and 4 Caucasian). SD Cohorts 2, 3, and 4 (5, 80, and 160 mg SD) will consist of 8 subjects (4 Japanese and 4 Caucasian). For each MD cohort, 6 Japanese subjects and 3 Caucasian subjects will receive LY3337641, while 2 Japanese subjects and 1 Caucasian subject will receive placebo. For each SD cohort, 3 Japanese subjects and 3 Caucasian subjects will receive LY3337641, while 1 Japanese subject and 1 Caucasian subject will receive placebo. Investigational product (IP) will be administered orally. Cohorts 1, 2, and 3 may be conducted in parallel if the site is able to accommodate more than 1 cohort at a time; however, priority will be given to dose Cohort 1, since the timing of this cohort will determine the timing of the interim analysis. Cohort 4 will be started based on the safety assessment up to Day 3 (48 hours postdose) of Cohort 2. If the dose level/regimen for Cohort 1 is not tolerated or there is a need to dose more subjects to assess safety, a daily dose of 30 mg or less (QD or twice daily [BID]) may be given in Cohort 5 based on the findings from Cohort 1. This will be discussed and agreed upon by the investigator and the Lilly clinical pharmacologist. The randomization rules and procedures will be the same as Cohort 1.



Abbreviations: BID = twice daily; FU = follow-up; JP = Japanese; LY = LY3337641; Pb = placebo; QD = once daily.
*Dose, regimen, and subject number may change for optional cohort.

Figure JPDB.1. Study Design

6. TREATMENTS

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

Study Treatment Name	Treatment order in TFL
Pooled Placebo SD	1
LY3337641 5 mg SD	2
LY3337641 80 mg SD	3
LY3337641 160 mg SD	4
Pooled Placebo QD	5
LY3337641 30 mg QD (Day 1)*	6
LY3337641 30 mg QD (Day 15)*	7
LY3337641 TBD mg BID or QD	TBD

* Split by Day for vital signs and ECG data only.

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

Study Treatment Name	Treatment order in TFL
LY3337641 5 mg SD	1
LY3337641 30 mg QD (Day 1)	2
LY3337641 80 mg SD	3
LY3337641 160 mg SD	4
LY3337641 30 mg QD (Day 15)	5
LY3337641 TBD mg BID or QD	TBD

7. SAMPLE SIZE JUSTIFICATION

Up to 60 subjects may be enrolled so that approximately 36 to 48 subjects complete the study. The sample size is customary for Phase 1 studies evaluating safety, PK, and/or PD parameters and is not based on the power of statistical hypothesis tests. Subjects who are randomized but discontinue the study may be replaced in the same cohort and race (Japanese or Caucasian) at the discretion of the sponsor.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all subjects who received at least one dose of LY3337641 or placebo, and have at least one postdose safety assessment.

The "Pharmacokinetic" population will consist of all subjects who received at least one dose of LY3337641 and have evaluable PK data.

The "Pharmacodynamic" population will consist of all subjects who received at least one dose of LY3337641 or placebo and have evaluable PD data

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, median, min, max and N; for log-normal data (e.g. the PK parameters: area under the concentration versus time curve [AUC] and maximum observed drug concentration [C_{max}]) the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all 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 will be also summarized by population (overall, Japanese and Caucasian) where appropriate.

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/subcategory, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized by population and listed. All other demographic data, including associated person demographics, will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

PK parameter estimates for LY3337641 will be calculated by standard noncompartmental methods of analysis. The PK analysis of this study will be the responsibility of Eli Lilly and Company.

9.3.2 Pharmacokinetic Statistical Methodology

Dose proportionality among the 5 mg, 30 mg (Day 1), 80 mg and 160 mg dose levels will be assessed using a power model.

The PK parameters C_{max}, $AUC_{0-\infty}$, and AUC_{0-24} will be assessed separately using a power model as follows:

$$\log(PK_i) = \alpha + \beta_i \cdot \log(dose_i) + \varepsilon_i$$

where i represents the ith subject, PK represents a pharmacokinetic parameter (AUC or C_{max}), and ε_i is a residual error term. The dose proportionality will be reported as the estimated ratio of dose-normalized means

$$\hat{R}_{dnm} = \left(\frac{h}{l}\right)^{\hat{\beta}_1 - 1}$$

and its 90% CI, where h and l denote the highest and lowest doses included in the model, respectively. The estimates of β along with its 90% CI, predicted geometric mean, and ratio of dose normalized geometric mean will be reported for each parameter.

The following SAS code will be used:

```
proc mixed data=pk;
    by parameter;
    model lpk = ldose / alpha=0.1 residual ddfm=kr;
    estimate 'xx mg' intercept 1 ldose yy / cl;
    estimate 'zz mg - xx mg' ldose pp / alpha=0.1 cl;
    ods output solutionf=est;
    ods output estimates=estims;
run;
```

The above analysis will be repeated for Japanese and Caucasian subjects seperatey to examine the effect of the population on dose proportionality.

The PK summary tables and figures will be the responsibility of Eli Lilly and Company.

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

Free Bruton's tyrosine kinase (BTK), total BTK, and BTK occupancy will be listed and summarized by population, treatment, and timepoint using standard descriptive statistics. BTK occupancy will be calculated as follows:

$$\text{BTK occupancy} = \frac{\text{Total BTK} - \text{Free BTK}}{\text{Total BTK}}$$

Change from baseline (Day 1 predose) in BTK occupancy will also be summarized and listed. Furthermore, mean and individual profiles of BTK occupancy will be presented over time.

Additional analysis will be performed if warranted upon review of the data.

9.4.2 Pharmacodynamic Statistical Methodology

Not applicable.

9.5 Pharmacokinetic/Pharmacodynamic Assessment

Exploratory graphical PK/PD analyses may be conducted to evaluate the relationship between LY3337641 concentrations (or exposure) and PD measures. Additional model-based analyses may be conducted if deemed appropriate. Any PK/PD analyses will be the responsibility of Eli Lilly and Company.

9.6 Safety and Tolerability Assessments

9.6.1 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 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. AEs by day of onset will be presented for Cohorts 1 and 5.

All AEs will be listed. Treatment-emergent AEs will be summarized by population, 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 population, 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.

9.6.2 Concomitant medication

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

9.6.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by population, treatment and timepoint, 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.

9.6.4 Vital signs

Vital signs data will be summarized by population and treatment together with changes from baseline, where baseline is defined as Day 1 predose. Figures of mean vital signs and mean changes from baseline profiles will be presented by population and treatment. Furthermore, values for individual subjects will be listed.

9.6.5 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR, QT, QRS duration and heart rate. In addition, QTcF (the QT interval corrected using Fridericia's formula) will be calculated as follows:

$$QTcF = \frac{QT}{\sqrt[3]{\left(60/HR\right)}}$$

The ECGs will be collected in triplicate; the mean of triplicates will be used in the analysis. The ECG data will be summarized by population and treatment together with changes from baseline, where baseline is defined as the mean of the Day 1 predose measurements. Figures of mean ECG data and mean changes from baseline will be presented by population and treatment. As

suggested by ICH E14 Guidline, the frequency of subjects with a maximum increase from baseline in QTcF interval will be summarized for each population and treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by population and treatment.

9.6.6 Other assessments

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

9.6.7 Safety and Tolerability Statistical Methodology

The relationship between concentrations of LY3337641 and changes from baseline QTcF (ΔQTcF) will be explored to assess the effect of LY3337641 concentration on the ΔQTcF. A scatter plot of the change from baseline in QTcF versus the concentrations with the fitted lines will also be plotted. A linear mixed-effects model will be fitted with the ΔQTcF as the response, the time-matched concentration as a covariate, population (Japanese/Caucasian) as a fixed effect, the population-by-concentration interaction term, and subject as a random effect. If there is no evidence of a difference between Japanese and Caucasian subjects, population will be removed from the model. The intercept and slope from the model along with their 90% CI will be reported. In addition, prediction intervals using C_{max} estimated at the highest given dose in the study will be reported together with its 90% prediction intervals.

Example SAS code:

```
proc mixed data=ecg alpha=0.1;
    class subject race;
    model change = conc race race*conc / cl solution ddfm=kr;
    random subject;
run;
```

10. INTERIM ANALYSES

The Lilly study team is unblinded. Data may be analyzed while the trial is ongoing, but no changes to the study design are planned. An assessment committee will not be formed.

Up to 3 interim analyses are planned to occur during the study according to the following timeframe: when at least safety and PK data of (1) Day 2 predose (24 hours after first dose) become available from at least 11 subjects in Cohort 1, including at least 4 Caucasian subjects; (2) Day 17 (48 hours after last dose) become available from Cohort 1; and (3) Day 29 become available from Cohort 1. All safety and PK data available from other cohorts by this time will be included in the interim analysis. The purpose of the interim analysis is to support the inclusion of Japanese subjects in future studies. The investigator and the Lilly clinical pharmacologist will review the safety and tolerability data, and the PK/PD scientist will review the PK data. The investigator will remain blinded, and the Lilly study team will be unblinded during this interim review.

Information that may unblind the study during the analyses will not be reported to study site or blinded personnel until the study has been unblinded.

Additional interim analysis may be conducted at any time throughout the study as required to ensure subject safety or to help guide dosing.

If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, clinical research physician/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

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.

3. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (E14), 12 May 2005.

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. time of maximum observed drug concentration (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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