I6T-JE-AMAD Statistical Analysis Plan

A Single-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of LY3074828 in Japanese and Caucasian Healthy Subjects.

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STATISTICAL ANALYSIS PLAN

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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]).

ADA	Antidrug antibody
AE	Adverse event
AUC	Area under the concentration versus time curve
AUC(0-∞)	Area under the concentration versus time curve from zero to infinity
BMI	Body Mass Index
C_{max}	Maximum observed drug concentration
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CRU	Clinical Research Unit
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
FU	Follow Up
ICH	International Conference on Harmonisation
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
TFLs	Tables, Figures, and Listings
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 11 August 2015), and Amendment (a) (final version dated 23 January 2018).

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 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

Primary Objective

The primary objective is to explore the safety and tolerability of LY3074828 in healthy Japanese and Caucasian subjects to define an appropriate dose for further clinical research in Japan.

Secondary Objectives

The secondary objectives of this study are

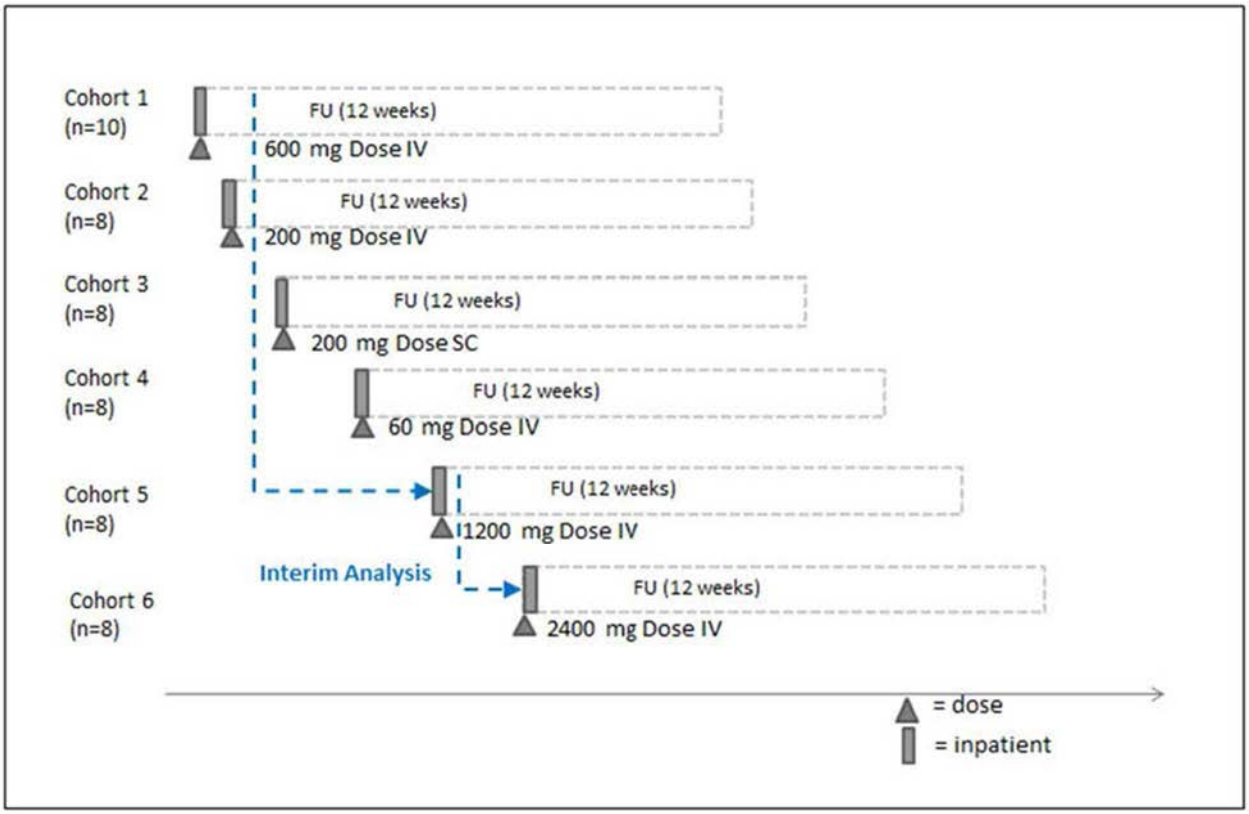
- to estimate the PK parameters of LY3074828 following intravenous (IV) and subcutaneous (SC) administration in healthy Japanese and Caucasian subjects.

- to explore the safety, tolerability, and PK of LY3074828 in Japanese subjects in relation to Caucasian subjects.

5. STUDY DESIGN

This is a single-site, subject- and investigator-blind, randomized, placebo-controlled, single-dose study to assess the safety, tolerability, and PK of LY3074828 in Japanese and Caucasian healthy subjects. Subjects will be randomized to LY3074828 or placebo within 1 of 6 cohorts, as shown in Figure 1. Cohort 1 will consist of 10 subjects (6 Japanese and 4 Caucasian) who will be randomized so that 5 Japanese subjects and 3 Caucasian subjects will receive LY3074828 while 1 Japanese subject and 1 Caucasian subject will receive placebo. Cohorts 2 through 6 will consist of 8 subjects (4 Japanese and 4 Caucasian) who are randomized in a 3:1 ratio of LY3074828 to placebo. For each cohort, 3 Japanese subjects and 3 Caucasian subjects will receive LY3074828 while 1 Japanese subject and 1 Caucasian subject will receive placebo.

Single doses up to 600 mg IV have been studied and shown to be well tolerated, therefore all cohorts, with the exception of Cohort 5 and Cohort 6, may be dosed in parallel if the site is able to accommodate more than 1 cohort at a time. Cohort 5 will be dosed after confirming the safety and PK data from Cohort 1. Cohort 6 will be dosed last after confirming the safety and PK data from Cohort 5. Two additional Japanese subjects will be included in Cohort 1 to ensure that a sufficient number of Japanese subjects will have received LY3074828 at the time of the interim analysis. An interim analysis is planned based on Cohort 1 data through Day 15 to support Japanese patients being included in the planned global Phase 2 study, Study I6T-MC-AMAC (AMAC).



Abbreviations: FU = follow up; IV = intravenous; SC = subcutaneous

Figure. 1 Study design

Treatment

Five IV dose levels and 1 SC dose level of LY3074828 will be assessed in Cohorts 1 through 6. The following treatments are planned:

Cohort 1: a single dose of LY3074828 600 mg or placebo IV
Cohort 2: a single dose of LY3074828 200 mg or placebo IV
Cohort 3: a single dose of LY3074828 200 mg or placebo SC
Cohort 4: a single dose of LY3074828 60 mg or placebo IV
Cohort 5: a single dose of LY3074828 1200 mg or placebo IV
Cohort 6: a single dose of LY3074828 2400 mg or placebo IV

6. TREATMENTS

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

Study Treatment Name	Treatment order in TFL
Placebo SC	1
Placebo IV	2
Pooled Placebo	3
60 mg LY3074828 IV	4
200 mg LY3074828 SC	5
200 mg LY3074828 IV	6
600 mg LY3074828 IV	7
1200 mg LY3074828 IV	8
2400 mg LY3074828 IV	9
Pooled LY3074828	10

7. SAMPLE SIZE JUSTIFICATION

Up to 60 subjects may be enrolled in order that approximately 50 subjects complete the study. It is intended that 10 subjects (6 Japanese and 4 Caucasian) will be randomized in Cohort 1, and 8 subjects (4 Japanese and 4 Caucasian) will be randomized in Cohorts 2, 3, 4, 5, and 6. The sample size is customary for Phase 1 studies evaluating safety, tolerability, and PK parameters.

Subjects who are randomized but not administered treatment or do not provide sufficient safety and/or PK data may be replaced if judged necessary by the Lilly clinical pharmacologist. The replacement subject should be assigned to the same treatment as the discontinued subject and should be Japanese or Caucasian to match the discontinued subject.

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 data from all randomized subjects receiving at least one dose of the study drug according to the treatment the subjects actually received.

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 [AUCs] 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 from subjects receiving placebo in the IV cohorts will be pooled to form 1 placebo group. Data will be also summarized by population (overall, Japanese and Caucasian) where appropriate. The clinical chemistry and hematology, vital signs, and electrocardiogram (ECG) data will only be summarized by population if a trend is observed.

Data analysis will be performed using SAS® Version 9.4.

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, population, ethnicity, race, body weight, height and body mass index (BMI) will be summarized by population and treatment and listed. All other demographic data will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK parameter estimates for LY3074828 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max} and area under the concentration versus time curve from zero to infinity [AUC(0-∞)] of LY3074828. Other noncompartmental parameters, such as half-life, clearance, and volume of distribution (apparent clearance and apparent volume of distribution for SC administration) may be reported.

9.3.2 Pharmacokinetic Statistical Methodology

The PK parameter estimates following IV administration will be evaluated to delineate effects of dose proportionality. Log-transformed C_{max} and AUC(0-∞) estimates will be evaluated in a power model with log-transformed dose as the explanatory variable. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence interval (CI).

Example SAS code 1:

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

The above analysis will also be repeated for each population separately to examine the effect of the population on dose proportionality.

For the SC dose, the bioavailability relative to IV infusion at the same dose will be evaluated via a log-transformed model. The log-transformed C_{max} and AUC(0-∞) will be the response variables, and route of administration (IV or SC) is the explanatory variable and ratio (SC/IV), and its 90% CI will be calculated based on the model to assess the absolute bioavailability.

Example SAS code 2:

```
proc mixed data=pk;
```

```
    by parameter;
    class route;
    model log_pk = route / residual ddfm=kr;
    lsmeans route / alpha=0.1 cl pdiff;
    ods output lsmeans=lsmeans;
    ods output diffs=diffs;
run;
```

Additional analysis will 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 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.

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 18.0 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. 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 March 2015). 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, where baseline is defined as Day -1. Individual values for 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 Immunogenicity

Immunogenicity data will be listed and the frequency of positive results will be summarized. Overlaying individual profiles of titer values will also be presented over time.

9.4.5 Vital signs

Vital signs data will be summarized by 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 by treatment will be presented by treatment. Furthermore, values for individual subjects will be listed.

9.4.6 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR, RR, QT, QTcB intervals, QRS duration and heart rate, where QTcB is the QT interval corrected using Bazett's formula. 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 ECG data will be summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose. Figures of mean ECG data and mean changes from baseline will be presented by treatment. The frequency of subjects with a maximum increase from baseline in QTcB and QTcF interval will be summarized for each treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects with QTcB and QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by treatment.

The relationship between concentrations of LY3074828 and changes from baseline QTcF (ΔQTcF) will be explored to assess the effect of LY3074828 concentration on the ΔQTcF. Where results are taken in triplicate, the mean of the measurements will be used in the analysis. A scatter plot of the change from baseline in QTcF versus the concentrations with the fitted lines will be plotted. A linear mixed-effects model will be fitted with the ΔQTcF as the response, the time-matched concentration as a covariate and subject as a random effect. The intercept and slope from the model along with their 90% CI will be reported.

9.4.7 Other assessments

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

9.4.8 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

The frist interim analysis is scheduled to occur when safety and PK data through Day 15 become available from at least 8 subjects in Cohort 1 including at least 3 Japanese subjects on LY3074828. 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 future inclusion of Japanese subjects in Study AMAC and to determine if dose escalation to 1200 mg should occur. The investigator and the Lilly study team will review the safety and tolerability data. The investigator will remain blinded and the Lilly study team will be unblinded during this interim review.

The data review for dose escalation to 2400 mg will not be included in the interim review.

An additional interim analysis may occur when safety and PK data through Day 15 becomes available from at least 6 subjects in Cohort 6, including at least 3 Japanese subjects. The purpose of this interim analysis is to support a future potential higher dosage in Study AMAG. The investigator and the Lilly study team will review the safety and tolerability data. The investigator will remain blinded and the Lilly study team will be unblinded during this interim review.

If antidrug antibody (ADA) follow-up described in the Protocol Addendum 1 is needed for subjects in Cohort 6, another interim analysis may occur when all procedures of the main protocol for Cohort 6 are completed, even if the ADA follow-up is in process. The investigator and the Lilly study team will review all available data. The investigator will remain blinded and the Lilly study team will be unblinded during this interim review.

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 and will be treated as missing for calculation of descriptive statistics.

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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