Statistical Analysis Plan I6T-MC-AMAL

A Phase 1, Single-Dose Study to Assess the Relative Bioavailability, Absolute Bioavailability, and Tolerability of LY3074828 Formulations in Healthy Subjects

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STATISTICAL ANALYSIS PLAN

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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	Anti-drug antibody
AE	Adverse event
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 time curve from zero to infinity
%AUC(tlast-∞)	Percentage of AUC(0-∞) extrapolated
BQL	Below the quantifiable lower limit of the assay
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL	Total body clearance of drug calculated after IV administration
CL/F	Apparent total body clearance of drug calculated after extra vascular administration
CRF	Case Report Form
CSR	Clinical Study Report
CRU	Clinical Research Unit
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
ED	Early discontinuation
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
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
SAP	Statistical Analysis Plan

SC	Subcutaneous
SD	Standard deviation
SOP	Standard Operating Procedure
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
VAS	Visual analog scale
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
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 15 December 2016).

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 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

- To evaluate the relative bioavailability of the LY3074828 lyophilized formulation prepared by reconstitution (Reference) and the extemporaneously prepared formulation (subcutaneous [SC] 2 × 1-mL) when administered to healthy subjects by SC injection.

4.2 Secondary Objectives

- To evaluate the relative bioavailability of LY3074828 extemporaneously prepared as the test formulation when the same volume is administered to healthy subjects by SC injection using a single injection (1 × 2-mL) and 2 injections (2 × 1-mL).
- To evaluate the absolute bioavailability of LY3074828 extemporaneously prepared as the test formulation when administered to healthy subjects by SC injection compared to intravenous (IV) infusion.
- To assess the impact of Drug Product formulation changes and number of injections on tolerability of LY3074828.

5. STUDY DESIGN

Study AMAL is a single-center, randomized, parallel-treatment, open-label, Phase 1 single-dose administration study evaluating LY3074828 in 72 healthy subjects.

Screening Period (≤4 weeks): Subjects will be evaluated for study eligibility ≤28 days prior to enrollment.

Residential Period (2 days): Subjects who fulfill the eligibility criteria will be randomized to 1 of 4 treatments, with 18 subjects randomized to each treatment, as shown below:

- Reference: 250 mg LY3074828; lyophilized reference formulation with 2 × 1-mL + 1 × 1.5-mL SC injections;
- Test SC 2 × 1-mL: 250 mg LY3074828; test formulation with 2 × 1-mL SC injections;
- Test SC 1 × 2-mL: 250 mg LY3074828; test formulation with 1 × 2-mL SC injection;
- Test IV: 250 mg LY3074828; test formulation by IV infusion over at least 30 minutes.

Subjects will report to the clinical research unit (CRU) on Day –1 and remain at the CRU until after the scheduled procedures have been completed on Day 2 as defined in the Schedule of Activities (Section 2 of Protocol). After randomization, study drug will be administered by either IV infusion or SC injection in the morning of Day 1 after an overnight fast. Subjects within the same enrollment group may be dosed across several days if required by the site for logistical or other purposes.

Outpatient Follow-up Period (approximately 14 weeks): The follow-up period will include outpatient visits for a total of 12 weeks following Day 1 dose administration to assess tolerability and PK of LY3074828. An end-of-study follow-up visit will be scheduled within 7 to 14 days after the last procedure or upon early discontinuation (ED).

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 TFL
250 mg LY3074828 reference SC (2 × 1 mL, 1 × 1.5 mL)	Reference	1
250 mg LY3074828 test SC (2 × 1 mL)	Test SC 2 × 1-mL	2
250 mg LY3074828 test SC (1 × 2 mL)	Test SC 1 × 2 mL	3
250 mg LY3074828 test IV	Test IV	4

7. SAMPLE SIZE JUSTIFICATION

A total of 72 subjects will be enrolled to ensure that approximately 64 subjects complete the study (16 completers per treatment). The estimated total variability (coefficient of variation) in AUC from time zero to infinity (AUC[0-∞]), AUC from time zero to time t, where t is the last sample with a measurable concentration (AUC[0-t_{last}]), and maximum observed drug concentration (C_{max}) was 49%, 49%, and 23%, respectively, in Study AMAA following a single SC dose of 120 mg LY3074828. The coefficient of variation of 49% was used for precision estimates and is assumed for all treatment arms. A sample size of 64 subjects will provide a precision of approximately 28% for the geometric means ratio in AUC(0 -∞), AUC(0-t_{last}), and C_{max} of reference to test in log scale. That is, there is a 90% probability that the half-length of the 90% confidence interval (CI) of the geometric means ratio in log scale is not larger than 28%.

Subjects who are randomized but not administered treatment may be replaced to ensure that approximately 64 subjects may complete the study.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all subjects who received study drug, and have at least one postdose safety assessment.

The "Pharmacokinetic" population will consist of all subjects who received study drug and have evaluable PK 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 (SD), median, min, max 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 analyses, 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, country of enrolment, site ID, 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 LY3074828 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	µg.day/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-∞)	µg.day/mL	area under the concentration versus time curve from zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
Cmax	µg/mL	maximum observed drug concentration
tmax	Hour	time of maximum observed drug concentration
$t_{1/2}$	Day	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
CL/F	L/day	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
CL	L/day	total body clearance of drug calculated after IV administration
V_Z	L	volume of distribution during the terminal phase after IV administration
V_{SS}	L	volume of distribution at steady state after IV administration
F		absolute subcutaneous bioavailability
Frel		relative bioavailability

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. For non-bolus, multiple dose profiles, the pre-dose 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 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.

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

Log-transformed C_{max}, AUC(0-∞), and AUC(0-t_{last}) estimates will be evaluated in a linear fixed-effect model with a fixed effect for formulation. Whether injection site leakage occurred (yes/no) may also be included in the model as a covariate if leakage occurs frequently. Furthermore, if this is found to be significant, the amount of leakage will also be added to the model. The formulation differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CI.

A single linear model with contrasts will be used for all of the following comparisons:

- Relative bioavailability of formulations: Test SC 2 × 1-mL versus Reference

- Relative bioavailability of number of injections: Test SC 2 × 1-mL versus Test SC 1 × 2-mL

If the number of injections is not observed to have an effect based on the above analysis, the following comparison will evaluate absolute bioavailability (on AUC[0-∞], and AUC[0-t_{last}] only):

- Test SC (combined data from SC 2 × 1-mL and SC 1 × 2-mL) versus Test IV

If the number of injections is observed to have an effect, analyses to evaluate absolute bioavailability will be done separately:

- Test SC 1 × 2-mL versus Test IV
- Test SC 2 × 1-mL versus Test IV

If the number of injections is observed to have an effect, the primary analysis of absolute bioavailabilty will be considered as that including SC 1 × 2-mL.

Example SAS code:

```
proc mixed data=pk;
    by parameter;
    class formulation ISLoccur;
    model log_pk = formulation ISLoccur ISLamount / residual ddfm=kr;
    lsmeans formulation / alpha=0.1 cl pdiff;
    ods output lsmeans=lsmeans;
    ods output diffs=diffs;
run;
```

The t_{max} will be analyzed using a Wilcoxon rank sum test for the relative bioavailability comparisons. Estimates of the median difference, 90% CIs, and p-values from the Wilcoxon rank sum test will be calculated.

Additional analyses may be conducted if they are 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 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 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

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.

9.4.5 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR, 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.

9.4.6 Injection/Infusion Site Assessment

Injection/infusion site assessment data (erythema, induration, categorical pain, pruritus and edema) will be listed and summarized in frequency tables.

9.4.7 Injection Site Pain Assessment

Injection site pain will be assessed using the Visual Analog Scale (VAS) and listed and summarized by treatment (performed only on subjects randomized to Test SC 2 × 1 mL and Test SC 1 × 2 mL).

9.4.8 Injection Site Leakage

Injection site leakage data will be listed. Any bleeding from injection site will also be documented (performed only on subjects randomized to Test SC 2 × 1 mL and Test SC 1 × 2 mL).

9.4.9 Immunogenicity

Immunogenicity data will be listed and frequency tables will be presented. The frequency of treatment-emergent anti-drug antibodies (ADAs) will also be calculated. Treatment-emergent ADAs are those that are induced or boosted by exposure to study drug, with a 4-fold increase in titer compared to baseline if ADAs were detected at baseline or a titer 2-fold greater than the minimum required dilution (1:10) if no ADAs were detected at baseline.

To show the association of treatment -emergent ADAs with adverse events, the frequency of treatment-emergent ADAs will be presented by MedDRA preferred term. Relationship between the presence of antibodies and the PK parameters of LY3074828 may be assessed graphically.

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

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

Interim analysis is scheduled to occur when safety and PK data through approximately Day 57 (8 weeks postdose) become available from enrolled subjects from each treatment. The purpose of the interim analysis is to: trigger Chemistry, Manufacturing, and Control processes with respect to LY3074828 formulation; trigger the formal bridging study; and to inform dose selection for Phase 3 first registration.

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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