Statistical Analysis Plan I6T-MC-AMBD

A Single-Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of LY3074828 in Healthy Chinese 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]).

AE	Adverse event
ADA	Anti-drug antibody
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
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 time zero to infinity
%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
BMI	Body mass index
BQL	Below the lower limit of quantification
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*)
F	Fraction of extravascular dose reaching the general circulation compared to an IV administration
ICH	International Conference on Harmonisation
IV	Intravenous
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities

MRE	Magnetic resonance elastography
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOP	Standard Operating Procedure
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TBL	Total bilirubin
CCI	[redacted]
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state after intravenous 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 10 July 2018) and protocol amendment (a) (final version dated 19 September 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 OBJECTIVE

4.1 Primary Objective

- To assess the safety and tolerability of single LY3074828 intravenous (IV) doses (300, 600, and 1200 mg) and single subcutaneous (SC) doses (200 and 400 mg) in healthy Chinese subjects.

4.2 Secondary Objective

- To evaluate the PK of single LY3074828 IV doses (300, 600, and 1200 mg) and single SC doses (200 and 400 mg) in healthy Chinese subjects.

CCI [redacted]

5. STUDY DESIGN

Study I6T-MC-AMBD is a single-center, subject- and investigator-blinded, randomized, parallel-group, placebo-controlled, Phase 1 single-dose study of LY3074828 in healthy Chinese subjects. Safety, tolerability, and PK of LY3074828 will be evaluated.

Native Chinese subjects born in China will be enrolled; all 4 biological grandparents and both biological parents must be of Chinese origin. Every effort should be made to enroll subjects so that at least 4 subjects in each cohort will be female. However, if the desired number of female subjects is not achieved, this will not constitute a protocol deviation.

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

Residential Period (3 days/2 nights): A total of approximately 60 subjects (12 subjects per cohort) who fulfil the eligibility criteria will be enrolled into the study. Subjects will be randomized within each cohort to receive study drug or placebo:

- Cohort 1: a single dose of LY3074828 300 mg or placebo IV infused over at least 30 minutes (10 LY3074828, 2 placebo)
- Cohort 2: a single dose of LY3074828 600 mg or placebo IV infused over at least 60 minutes (10 LY3074828, 2 placebo)
- Cohort 3: a single dose of LY3074828 1200 mg or placebo IV infused over at least 2 hours (10 LY3074828, 2 placebo)
- Cohort 4: a single dose of LY3074828 200 mg or placebo SC (10 LY3074828, 2 placebo)
- Cohort 5: a single dose of LY3074828 400 mg or placebo SC (10 LY3074828, 2 placebo)

Dosing of cohorts may be conducted in parallel or sequentially at the discretion of the investigator. Subjects will report to the clinical research unit (CRU) on Day -1. After randomization, study drug will be administered by investigative site staff by IV administration using a forearm vein or SC injection in the abdomen using pre-filled syringes (PFSs) in the morning of Day 1 after an overnight fast. Subjects will remain at the CRU until the scheduled procedures have been completed on Day 2, and will then be discharged.

Outpatient Follow-up Period (12 weeks): The follow-up period will include outpatient visits for a total of approximately 12 weeks (Days 4, 8, 11 [SC only], 15, 22, 29, 43, 57, 71, and 85) following dose administration on Day 1 to assess the safety, tolerability, and PK of LY3074828 in healthy Chinese subjects.

6. TREATMENTS

The following is a list of the study treatment abbreviations that will be used in the TFLs. Placebo IV and Placebo SC data may be pooled in the TFLs, as appropriate.

Study Treatment Name	Treatment order in TFL
Placebo IV	1
300 mg LY3074828 IV	2
600 mg LY3074828 IV	3
1200 mg LY3074828 IV	4
Placebo SC	5
200 mg LY3074828 SC	6
400 mg LY3074828 SC	7

7. SAMPLE SIZE JUSTIFICATION

Sixty subjects who fulfil the eligibility criteria may be enrolled into the study to try to ensure that approximately 50 subjects (10 subjects per cohort) complete. The number of subjects in Study AMBD is not sufficient for any formal ethnic comparison, but the safety, tolerability, and PK data will be assessed in Chinese subjects and will be used to support the inclusion of Chinese subjects in future studies involving LY3074828.

The sample size is customary for Phase 1 studies evaluating safety and PK, and is not powered on the basis of statistical hypothesis testing.

Subjects who withdraw from the study will not be replaced. For analytical purposes, a subject's study participation is considered as complete if he/she receives the study drug as per the protocol requirements and completes all activities up to and including at least Day 57.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled subjects who received LY3074828 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 LY3074828 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: area under the concentration 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 time point. 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.

No adjustments for multiple comparisons will be made.

Data analysis will be performed using SAS® Version 9.4 or greater.

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index (BMI) will be summarized and listed. All other demographic variables, including associated person demographics, will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK parameter estimates will be determined for LY3074828 using non-compartmental procedures with a validated software program CCI [redacted]

Serum concentrations of LY3074828 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	day*µg/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-∞)	day*µg/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	µg/mL	maximum observed drug concentration
t_{max}	day	time of maximum observed drug concentration
$t_{1/2}$	day	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
CL	L/day	total body clearance of drug calculated after extra-vascular administration
CL/F	L/day	apparent total body clearance of drug calculated after IV administration
V_z	L	volume of distribution during the terminal phase after IV administration
V_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration
V_{ss}	L	volume of distribution at steady state after IV administration
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration
F	%	absolute bioavailabilty
F (pooled)	%	absolute bioavailability of pooled 200 mg and 400 mg SC treatments

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.

Estimates of absolute bioavailability will be made as follows:

$$F = . \frac{\text{Geo Mean } AUC(0-\infty)/D \text{ (200 mg or 400 mg SC)}}{\text{Geo Mean } AUC(0-\infty)/D \text{ (pooled 300 mg, 600 mg \& 1200 mg IV)}} \times 100$$

and

$$F \text{ (pooled)} = \frac{\text{Geo Mean } AUC(0-\infty)/D \text{ (pooled 200 mg \& 400 mg SC)}}{\text{Geo Mean } AUC(0-\infty)/D \text{ (pooled 300 mg, 600 mg \& 1200 mg IV)}} \times 100$$

where AUC(0-∞)/D = AUC(0-∞) divided by dose.

CCI [redacted]

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times which will be set to zero.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive 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 serum concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on the observed last quantifiable drug concentration (C_{last}) will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantification (BQL). Serum 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 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

No formal statistical analysis will be performed for this study. The PK parameters will be summarized by treatment and listed.

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 (TEAE) is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs and product complaints will be listed. TEAEs 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 TEAEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 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 listed.

9.4.2 Concomitant medication

Concomitant medication will be coded using the World Health organization (WHO) drug dictionary (Version March 2018). 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. Changes from baseline (Day -1) will also be presented. 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 will be presented by treatment.

Furthermore, values for individual subjects will be listed.

9.4.5 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes and will not be presented. Any clinically relevant findings will be reported as an AE.

9.4.6 Subcutaneous Injection-site Reaction

Injection-site reactions will be evaluated for SC treatments through the collection of pain assessments and specific site assessments for local tolerability, which will evaluate erythema, induration, categorical pain, pruritus, and edema. Data from injection-site evaluations (including pain), which are recorded as a result of specific questionnaires, will not be reported as AEs. However injection site reactions may be reported as adverse events if: a) spontaneously reported by a subject or b) at the discretion of the principal investigator.

Injection-site reaction data will be listed and summarized by treatment in frequency tables.

9.4.7 Subcutaneous Injection-site Pain

Intensity of pain data will be quantified using a 100-mm validated VAS for SC treatments. The data will be listed and summarized by treatment and time point. Furthermore, scatter plots of the 0 minute, 15 minute, and 30 minute VAS scores will be presented by treatment and time point.

9.4.8 Subcutaneous Injection-Procedure Evaluation

Any bleeding or bruising at the injection site will be listed.

CCI [redacted]

9.4.10 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥2× ULN, liver tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

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

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by treatment and listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual subject data listings.

9.4.11 Hypersensitivity Reactions

Hypersensitivity reactions will be evaluated by examination of TEAEs and serious AEs, and through the use of a follow-up form which will be completed by the investigator. Data from the follow-up form will be listed. Furthermore, the subjects' medical history and associated person medical history data for drug hypersensitivity and infusion related reactions will be listed.

9.4.12 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim statistical analyses are planned. If an unplanned interim analysis is deemed necessary, the Lilly CP, CRP/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.

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. No imputation of data will be applied unless otherwise stated.

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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