J2F-MC-OHAA Statistical Analysis Plan

A Single Ascending Dose Study to Evaluate Safety, Tolerability, and Pharmacokinetics of LY3478006 in Healthy Subjects

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STATISTICAL ANALYSIS PLAN

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Study Drug: LY3478006

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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]).

AE	Adverse event
ADA	Antidrug antibody
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
$AUC_{0-\infty}$	Area under the concentration versus time curve from time zero to infinity
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL	Total body clearance of drug
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
F	Bioavailability of drug
ICH	International Conference on Harmonisation
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
NCA	Noncompartmental methods of analysis
NGF	Nerve growth factor
PK	Pharmacokinetic
pTrkA	Phosphorylated tropomyosin receptor kinase
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
TBL	Total bilirubin
TE ADA	Treatment-emergent antidrug antibody

TFLs	Tables, Figures, and Listings
tTrkA	Total Tropomyosin receptor kinase
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state following IV administration
V_z	Volume of distribution during the terminal phase
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 04 November 2019).

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 with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. 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 with Eli Lilly and Company 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 assess the safety and tolerability following single doses of LY3478006 in healthy subjects, including those of Japanese origin.

4.2 Secondary Objectives

- To assess the serum PK of LY3478006 following single intravenous **(**IV) or subcutaneous (SC) doses of LY3478006 in healthy subjects.
- To estimate the absolute bioavailability of LY3478006 following a single SC dose relative to a single IV dose in healthy subjects.

4.3 Exploratory Objectives

- To assess the changes in serum nerve growth factor (NGF) levels following single IV and SC doses of LY3478006 in healthy subjects.
- To assess the changes in skin phosphorylated TrkA (pTrkA) and total TrkA (tTrkA) levels following single IV and SC doses of LY3478006 in healthy subjects.

- To assess the serum PK of LY3478006 following single IV doses of LY3478006 in healthy Japanese subjects.

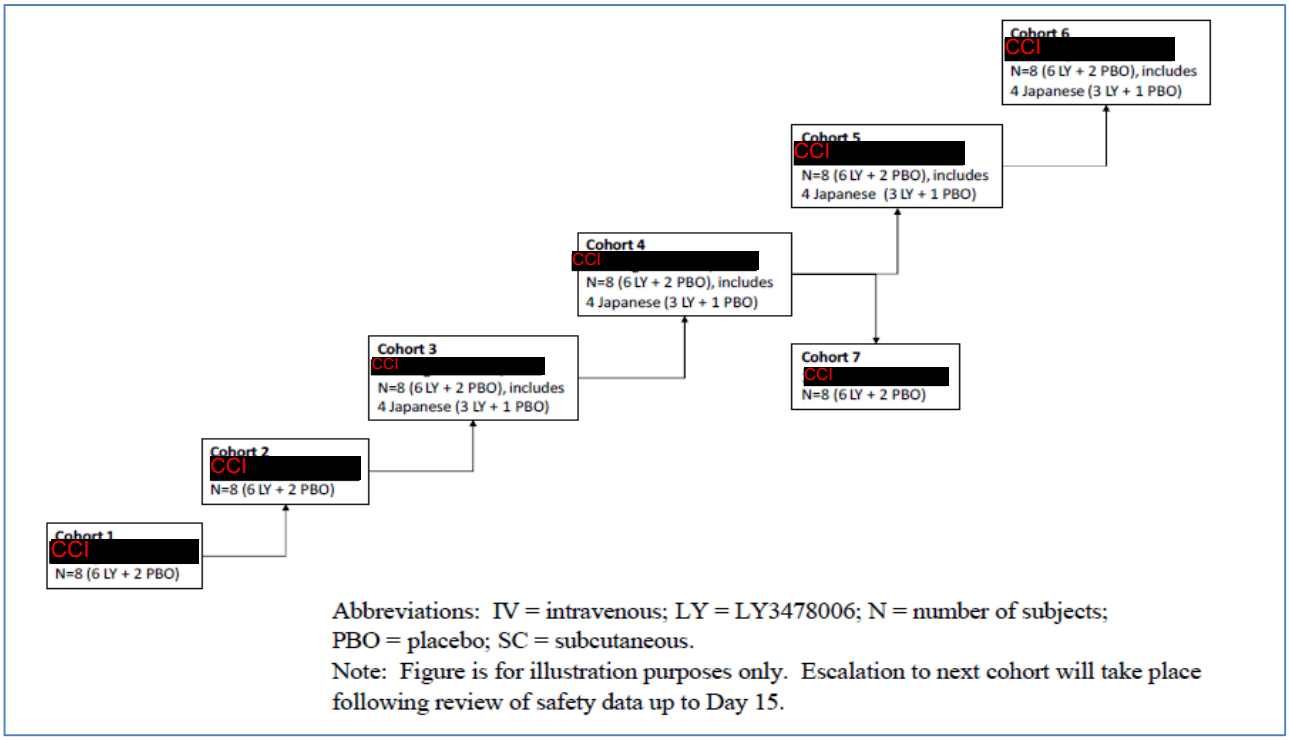
5. STUDY DESIGN

Study J2F-MC-OHAA is a Phase 1, subject- and investigator-blind, placebo-controlled, randomized, parallel, single-ascending dose study in healthy subjects.

Seven cohorts (Cohorts 1 to 7) of healthy subjects will be studied. In each cohort, 8 subjects will be randomized (3:1 ratio) to receive LY3478006 or placebo (6 LY3478006 subjects and 2 placebo subjects). Four of the 8 healthy subjects enrolled in Cohorts 3, 4, 5, and 6 are planned to be of Japanese origin (first generation; randomized [3:1 ratio] to receive LY3478006 or placebo). If the recruitment of Japanese subjects becomes limiting for a particular cohort, then additional non-Japanese subjects may be entered into a cohort to allow for dose escalation. Japanese subjects will subsequently be enrolled so that at least 3 Japanese subject's complete placebo and each LY3478006 dose level. In addition, it is preferred that the non-Japanese subjects also be non-Asian.

Cohorts 1 through 6 will be sequentially enrolled to test 6 single ascending dose levels of LY3478006 CCI [redacted]) or placebo administered IV. Subjects in Cohorts 1 through 6 may be dosed in at least 2 dosing groups (approximately 4 subjects in each group) on separate days. Study drug will be administered to 1 subject at a time (study drug infusion can start for a given subject after the end of infusion of the previous subject). Safety data through Day 15 postdose must be evaluated from at least 6 of 8 subjects prior to the decision to dose escalate to the subsequent cohort. Cohort 7 will be enrolled to test 1 dose level of LY3478006 CCI [redacted] or placebo administered SC. All subjects in Cohort 7 may be dosed on a single day.

Figure 1 study design.



6. TREATMENTS

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

Study Treatment Name	Treatment order in TFL
Placebo IV	1
Placebo SC	2
CCI LY3478006 IV	3
CCI LY3478006 IV	4
CCI LY3478006 IV	5
CCI LY3478006 SC*	6
CCI LY3478006 IV	7
CCI LY3478006 IV	8
CCI LY3478006 IV	9

*CCI will be replaced with actual dose received by the subjects and doses will be presented in ascending order.

7. SAMPLE SIZE JUSTIFICATION

Up to 70 healthy subjects may be enrolled such that approximately 56 subjects complete the study. It is planned that 16 of these 56 subjects will be of Japanese origin (first-generation). Subjects who are randomized but not administered treatment may be replaced to ensure that enough subjects complete the study. The ethnicity of the replacement subject (Japanese or non-Japanese) should match the ethnicity of the discontinued subject, where possible.

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

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 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

Summary statistics and figures by ethnicity (Japanese and non-Japanese) will be provided as appropriate.

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 [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 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 will be summarized by ethnicity (overall, Japanese and Non-Japanese) and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

PK parameters for LY3478006 will be calculated by standard noncompartmental methods of analysis (NCA) using Phoenix/WinNONLIN. The primary parameters for analysis will be C_{max} and area under the concentration versus time curve from zero to infinity ($AUC_{0-\infty}$). Other noncompartmental parameters, such as halflife ($t_{1/2}$), total body clearance of drug (CL), volume of distribution during the terminal phase (V_z) (apparent clearance, and apparent volume of distribution for SC administration) may be calculated and reported as deemed appropriate.

Eli Lilly is responsible for the PK statistical analysis and reporting of data.

In addition, LY3478006 concentration time data may be analyzed using non-linear mixed effect modeling as implemented in software such as NONMEM. Serum data from all subjects will be pooled to determine the compartmental PK parameters (for example, CL, volume of distribution at steady state following IV administration [V_{ss}], t1/2, bioavailability of drug [F]) and between-subject variability. Covariate relationships, such as CL or volume of distribution versus body size (for example, body weight and body mass index) or gender, may be investigated through graphical exploration and may be quantified through modeling. The effect of factors such as race/ethnicity (Japanese versus non-Japanese subjects) could be tested in the model and may be included in the final model.

9.3.2 Pharmacokinetic Statistical Methodology

PK parameter estimates from the NCA will be evaluated to delineate effects of dose proportionality. Log-transformed C_{max} and AUC estimates will be evaluated in a linear model with log-transformed IV dose as a fixed effect. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence intervals (CI). 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 will be the response variable, and route of administration (IV/SC) is the explanatory variable.

Eli Lilly is responsible for the PK statistical analysis and reporting of data.

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 ethnicity (overall, Japanese and non-Japanese), 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 ethnicity (overall, Japanese and Non-Japanese), treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 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 by the investigator. Any serious AEs will be listed.

Discontinuations due to AEs will be listed.

9.4.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version September 2019). 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 and flagged on 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 the Day 1 predose assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

Values for individual subjects will be listed.

9.4.5 Electrocardiogram (ECG)

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

9.4.6 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 medications that have potential for hepatotoxicity, including acetaminophen will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and biopsy assessments 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.

9.4.7 Immunogenicity Assessments

The frequency and percentage of subjects with pre-existing antidrug antibody (ADA) and with treatment-emergent ADAs (TE ADA) to LY3478006 will be tabulated and listed.

For subjects who are ADA negative at baseline, TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution of the assay. For subjects who are ADA positive at baseline, TE ADAs are defined as those with a 4-fold (2 dilution) increase in titer compared to baseline. The frequency and percentage of subjects with cross-reactive and neutralizing antibodies, if measured, may also be tabulated for subjects with TE ADA.

The relationship between the presence of antibodies and the PK parameters may be assessed.

Eli Lilly is responsible for the immunogenicity reporting of data.

9.4.8 Allergic/Hypersensitivity reactions

For all allergic and drug hypersensitivity reactions that occur, additional follow-up data will be collected to assess the patient's medical history, alternative causes, and symptoms. These data will be listed.

9.4.9 Injection/Infusion Site Reactions

Injection-site reaction data will be listed and summarized by ethnicity (overall, Japanese and non-Japanese) and treatment in frequency tables. The reaction data may include erythema, induration, pain, pruritus, and edema.

9.4.10 Neurological Examinations

New or worsened abnormality on the neurologic exam should be reported as an AE and listed. Neurological examination data will be listed for all subjects by treatment and timepoint.

9.4.11 Pupillometry Assessments

Pupillometry data will be listed for all subjects by treatment and timepoint.

9.4.12 Biomarkers

Abdomen skin biopsy samples will be collected to study protein biomarkers, including tTrkA and pTrkA. The protein biomarkers data will be summarized by ethnicity (overall, Japanese and Non-Japanese) and treatment and listed.

Eli Lilly is responsible for the biomarkers statistical analysis and reporting of data.

9.4.13 Serum NGF levels

Serum NGF levels will be evaluated over time to assess changes in NGF levels and will be listed by subject.

Summary tables, with changes from baseline where baseline is defined as the Day 1 predose assessment, mean (+ SD) figures, overlaying individual figures will be provided for the serum NGF levels by ethnicity (overall, Japanese and Non-Japanese).

Eli Lilly is responsible for the serum NGF levels statistical analysis and reporting of data.

9.4.14 Other assessments

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

9.4.15 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. Data Review During the Study

Data will be reviewed during the study to evaluate the safety and PK of LY3478006, inform dose selection/escalation decisions, and confirm inclusion of data from an adequate number of Japanese and non-Japanese subjects.

Interim data reviews are planned as follows:

- Prior to initiating the planned CCI SC dose level cohort (Cohort 7), it will include
  - PK and safety data from Cohorts 1, 2, and 3 (CCI [redacted])
- Prior to initiating the CCI dose cohort (Cohort 6), or a SC dose level cohort (Cohort 7), it will include:
  - PK data from Cohorts 1, 2, 3, and 4 (CCI [redacted])
  - Available safety data from Cohorts 1, 2, 3, 4, and 5 (CCI [redacted]) Safety data from Cohort 5 will not be required for the CCI SC dose level cohort (Cohort 7) decision.

11. INTERIM ANALYSES

No interim statistical analyses are planned.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13. 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.

14. DATA PRESENTATION

14.1 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.

14.2 Missing Data

Missing data will not be displayed in listings.

14.3 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 center of the table, such as, “No serious adverse events occurred for this study.”

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