Statistical Analysis Plan: I9F-MC-SCAA

Single-Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3323795 in Healthy Subjects

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1. Statistical Analysis Plan: I9F-MC-SCAA: Single Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3323795 in Healthy Subjects

Confidential Information

LY3323795

A Phase 1 study of LY3323795 in healthy subjects that will be conducted in 3 parts. Parts A and B are subject- and investigator-blind, placebo-controlled, randomized studies. Part A is a single ascending dose, 3-period, 2-cohort, crossover study to assess the safety, tolerability, and plasma pharmacokinetics (PK) and pharmacodynamics (PD) of LY3323795 in healthy volunteers. Part B is a single-dose, 3-cohort study to assess the safety, tolerability, and the plasma and cerebrospinal fluid (CSF) PK and PD of LY3323795. Part C is an open label, 2-period, fixed-sequence study in healthy volunteers to evaluate a potential cytochrome P450 (CYP) 3A4 interaction when LY3323795 is coadministered with itraconazole.

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Phase 1 Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 20-Dec-2016 GMT

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3. Revision History

Statistical Analysis Plan, Version 1 was approved prior to any data being received in-house and unblinding.

4. Objectives

4.1. Primary Objective

The primary objective of this study is to explore the safety and tolerability of single doses of LY3323795 in healthy subjects.

4.2. Secondary Objectives

The secondary objectives of this study are:

- To explore the plasma and cerebrospinal fluid (CSF) pharmacokinetics (PK) of single doses of LY3323795.
- To explore the plasma and CSF pharmacodynamics (PD) of single doses of LY3323795.

4.3. Exploratory Objectives

5. Summary of Study Design

Study I9F-MC-SCAA (SCAA) is a Phase 1 study in healthy subjects that will be conducted in 3 parts, as follows:

- Part A will be a subject- and investigator-blind, placebo-controlled, randomized, single ascending dose, 3-period, dose-escalation study to evaluate safety, tolerability, and plasma PK/PD of LY3323795.
- Part B will be a subject- and investigator-blind, placebo-controlled, randomized, single-dose, single-period, lumbar catheter study with up to 3 cohorts/dose levels to evaluate the central and plasma PK/PD of LY3323795.
- Part C will be an open-label, 2-period, fixed-sequence, single-cohort study to evaluate a potential cytochrome P450 (CYP) 3A4 interaction when LY3323795 is coadministered with itraconazole.

5.1. Determination of Sample Size

The sample size of 9 in each cohort of Part A is customary for Phase 1 studies evaluating safety, PK, and/or PD parameters, and is not based on statistical mean estimation.

For Part B, given the CSF Aβ variability observed in prior studies that measured CSF Aβ, the sample size of 5 subjects per LY3323795 dose and 2 subjects per placebo in a parallel cohort, pooled placebo design is sufficient to detect a mean Aβ reduction of approximately 21% or more from baseline. Assuming a standard deviation of 22% for the CSF $A\beta_{1\text{-}40}$, a sample size of 5 subjects per dose would provide approximately 90% coverage probability that the half-width of the 80% confidence interval (CI) for the mean of percentage change from baseline of CSF $A\beta_{1\text{-}40}$ would be within 21%. For example, if the estimate of the percentage change from baseline CSF $A\beta_{1\text{-}40}$ at nadir concentration (C_{nadir}) is 50%, then the confidence limit for the percentage change from baseline would be (29%, 71%).

For Part C, assuming a within-subject variability of 25% for the PK parameter (area under the drug plasma concentration versus time curve [AUC] or maximum concentration [C_{max}]) of LY3323795, a sample size of 8 subjects would provide approximately 90% coverage probability that the half-width of the 90% CI for the geometric mean ratio of LY3323795 with itraconazole, compared with LY3323795 alone, would be within 0.3 in log scale, or 1.35 in natural scale. For example, if the estimate of the ratio of LY3323795 with itraconazole over LY3323795 alone is 1.2, then the confidence limit would be (88%, 162%).

Subjects who drop out may be replaced at the discretion of the sponsor and investigator to achieve protocol-required completers. In Part A, a replacement subject's treatment assignment will follow that of the subject being replaced but may not require completion of all study periods. In Part B, a replacement subject's treatment assignment will follow that of the subject being replaced. In Part C, all subjects, and any replacements, will be on the same treatment assignment.

5.2. Method of Assignment to Treatment

For Cohorts 1 and 2 in Part A, up to approximately 24 subjects may be enrolled so that approximately 18 subjects (9 subjects per cohort [6:3, LY3323795:placebo per dose level]) complete the study.

For Cohorts 3 to 5 in Part B, up to approximately 30 subjects may be enrolled so that approximately 21 subjects (7 subjects per cohort [5:2, LY3323795:placebo]) complete the study.

For Cohort 6 in Part C, up to 12 subjects may be enrolled so that approximately 8 subjects complete the study. Part C is open label study.

Randomization tables for allocation of LY3323795 and placebo will be prepared by the Lilly statistician.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or designee.

It is planned that all safety reporting including eye safety assessments will be conducted by Covance; with the exception of inferential analyses on safety, PK, PD, and biomarkers, which will be conducted by Eli Lilly and Company.

Pharmacokinetic and pharmacodynamic analyses will be conducted on the full analysis set. This set includes all data from all subjects receiving at least 1 dose of the investigational product. Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. As this is a Phase 1 study and there will be no formal statistical hypothesis testing, any changes to the planned analysis will not necessitate a protocol amendment and will be detailed in the study report.

Unless otherwise stated, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.10 (0.05 each side).

6.2. Multicenter Studies

Due to this being a primarily safety and tolerability study with as single investigation center and low patient numbers per dose, there is no plan to fit center as a covariate in any of the models.

The demographic/disposition listings will make it clear as to which site each patient was attributed.

6.3. Multiple Comparisons/Multiplicity

No adjustments for multiplicity will be made.

6.4. Patient Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

6.5. Patient Characteristics

The patient's age, sex, race, weight, body mass index (BMI), height, smoking habits, or other demographic characteristics will be recorded and may be used in the PK, PD, and safety analyses as quantitative or classification variables. These characteristics will be listed and summarized at baseline, with the exception of weight which will also be summarized over time.

6.5.1. Subgroup Analyses

Any subgroup analyses will be exploratory (post hoc) in nature.

6.6. Concomitant Therapy

Concomitant therapy will be listed and summarized.

6.7. Extent of Exposure

Dosing information for each individual subject will be listed.

6.8. Safety Analyses

6.8.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur prior to randomization will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activity (MedDRA).

The number of investigational product–related serious adverse events (SAEs) will be reported.

A listing of all patients' laboratory values and a listing of abnormal laboratory values (for that parameter) during the treatment period will be provided, and results will be summarized.

6.8.2. Statistical Evaluation of Safety

The safety analyses will be conducted for Part A, B, and C separately. The safety and tolerability of treatment will be assessed by summarizing the following:

- Adverse Events
    - Treatment-emergent adverse events (TEAEs) by:
        - System Organ Class (SOC) and Preferred Term (PT)
        - Maximum severity
        - Considered to be related to investigational produce by investigator
    - Serious Adverse Events (SAEs)
    - Adverse events (AEs) leading to discontinuation
- Vital signs and weight
- Laboratory measurements
- Electrocardiograms (ECGs)
- Eye assessments

Safety parameters will be listed and summarized using standard descriptive statistics, where appropriate. Additional analysis will be performed, if warranted, upon review of the data.

6.8.2.1. Adverse Events

Treatment-emergent adverse events are defined as the reported AEs that first occurred or worsened during the postbaseline phase, compared with baseline phase. For each TEAE, the severity level of the event (mild, moderate, or severe) will be determined by patient or physician opinion. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. For each LLT, the maximum severity at baseline will be used as the baseline severity. If the maximum severity during postbaseline is greater than the maximum baseline severity, the event is considered to be treatment-emergent for the specific postbaseline period. For each patient and TE AE, the maximum severity for the MedDRA level being displayed (PT, High Level Term [HLT], or SOC) is the maximum postbaseline severity observed from all associated LLTs mapping to that MedDRA level. For events that are gender-specific, the denominator and computation of the percentage will include only patients from the given gender.

6.8.2.2. Eye Assessment

Eye testing will include distance and near visual acuity (best-corrected or pinhole using the Snellen Chart and Near Reading Card), Humphrey visual field testing (using the 10-2 protocol with a red-on-white target), and ophthalmoscopy.

Only subjects who pass all other inclusion/exclusion criteria at screening should be sent for these eye examinations. Results from subsequent eye tests during the study will be compared with the screening results to track any changes in subjects' vision.

For each method of eye assessment, change from baseline (Yes/No) and change from baseline clinically significant (Yes/No) will be listed, and if there are sufficient changes they will be summarized by treatment group and compared with Fisher's exact test.

6.8.2.3. Laboratory Tests

The listing of patients with abnormal high or low laboratory values, based on Covance reference ranges, at any time postbaseline will be created.

The listing of patients with elevations in hepatic laboratory tests as defined below will be created.

- An alanine aminotransferase (ALT) or aspartate aminotransferase (AST) measurement greater than or equal to 3 times (3×) the Covance upper limit of normal (ULN) during the treatment period.
- A total bilirubin measurement greater than or equal to 2 times (2×) ULN during the treatment period.

6.8.2.4. Vital Signs and Weight

Plot of vital signs and weight over time will be created for each patient.

6.8.2.5. Electrocardiogram Intervals and Heart Rate

Analysis of corrected QT (QTc) data from ECG monitoring in a Phase 1 trial is performed to judge the extent and/or risk of QT prolongation. A scatter plot will be generated to explore the relationship between QTc and drug exposure, and will assess the mean change in QTc using

Fridericia's formula as a function of plasma drug concentration. The QTc analysis will not include ECGs collected in Part C (itraconazole interaction), due to the potential for non-LY3323795-induced changes in QTc. Frequency tables of QTc changes from baseline and large QTc values may also be obtained in accordance with International Conference on Harmonisation (ICH) guidance, and additional analyses may be conducted if required.

6.9. Pharmacokinetic Analyses

6.9.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3323795 will be calculated using standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max} and AUC of LY3323795. Other noncompartmental parameters, such as half-life ($t_{1/2}$), apparent clearance (CL/f), and apparent volume of distribution (V_D), may be reported.

Renal clearance of LY3323795 will be calculated as the ratio of amount excreted/AUC. This will be compared to the unbound glomerular filtration rate (GFR), which is estimated using creatinine levels.

In Part C, PK parameter estimates for itraconazole samples collected on Day 16 will be calculated using standard noncompartmental methods of analysis. Maximum concentration and AUC will be reported. Itraconazole concentrations collected as part of this study may be analyzed along with data collected in other studies as part of a larger assessment of itraconazole PK. If such an analysis is performed, the results of the analysis will be reported separately from the final report for this study. Concentrations of itraconazole metabolites may be characterized on an exploratory basis.

6.9.2. Pharmacokinetic Statistical Inference

In Part C, the area under the drug plasma concentration versus time from time zero to infinity ($AUC_{[0-\infty]}$) and C_{max} for LY3323795 administered alone and in the presence of itraconazole will be compared using an analysis of variance (ANOVA) model. The parameters will be log-transformed prior to analysis. The model includes a fixed effect for the treatment and a random effect for subject. The following model will be built: ln (PK parameter) = treatment + subject + random error, where treatment is a fixed effect with 2 levels: LY3323795 alone (reference) and LY3323795 with itraconazole (test).

The least square (LS) mean for each treatment and the 90% CI for the difference in means will be estimated from the ANOVA model and back-transformed from the log scale to provide estimates of the geometric means and 90% CIs for the ratio of the geometric means of LY3323795 + itraconazole versus LY3323795 alone.

The time to Cmax (tmax) parameter will be analyzed using the Wilcoxon-signed rank test. Median differences and 90% CIs for the difference between LY3323795 + itraconazole (test) and the LY3323795 alone (reference) will be calculated.

6.10. Pharmacodynamics Analyses

6.10.1. Pharmacodynamics Parameter Estimation

In Parts A and B, plasma concentrations of $A\beta_{1-40}$ and $A\beta_{1-42}$ will be summarized for each dose group based on the C_{nadir} and the time to reach C_{nadir} (t_{nadir}).

In Part B, CSF concentrations of $A\beta_{1-40}$, $A\beta_{1-42}$will be summarized for each dose group based on the C_{nadir}, t_{nadir}, and the 24-hour average values, expressed as a percentage change from baseline. CCI [redacted] Other parameters may be calculated, as appropriate.

6.10.2. Pharmacodynamics Statistical Inference

For Part B of this protocol, statistical analysis of CSF $A\beta_{1-40}$,$A\beta_{1-42}$, CCI [redacted] concentrations obtained over the fixed-scheduled sampling period will be analyzed using a repeated-measures analysis with the primary statistical inference of pairwise comparison of the overall mean difference among the LY3323795 doses and placebo using a 90% CI. The statistical model may include the baseline CSF $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations obtained during predose CSF collection period and fixed effects of dose groups (placebo and doses of LY3323795), scheduled CSF sampling time, and the interaction between dose groups and sampling times. A compound symmetric covariance structure may be used. From the statistical model, the primary statistical estimates will be the mean percentage reduction from baseline in CSF $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations at each time point with LY3323795 over the 36-hour sampling interval. The above model will fit both the log-transformed and percentage change from baseline in CSF $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations.

Additional exploratory analysis will be performed on plasma concentrations of TMEM27 with a similar statistical model.

6.11. Pharmacokinetic/Pharmacodynamic Analyses

It is intended that a compartmental modeling approach will be used to describe the plasma and CSF PK and CSF PD of LY3323795. Compartmental modeling will be performed using nonlinear mixed-effects modeling. Although it is not intended that the model will assess the impact of patient-specific factors (such as age, body weight, or race/subrace) on LY3323795 PK, these may be included, if appropriate. Modeling may be performed sequentially by first modeling plasma PK and then fixing the values from that model when developing a model to describe CSF PK. It is intended that an indirect response model will be used to characterize the PD effect of LY3323795 on CSF $A\beta_{1-40}$ formation, with PK parameters fixed to those values determined in previous steps. Other PD endpoints (eg, $A\beta_{1-42}$) may be modeled, if warranted.

Other modeling approaches or graphical analyses may be used, as deemed appropriate. The results of this modeling may not necessarily be included in the final study report.

Further details on the planned pharmacokinetic analyses can be found in the pharmacokinetic analysis plan.

6.12. Interim Analyses and Data Monitoring

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, clinical research physician (CRP)/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

Safety and/or PK Interim Access to Data (IAD) reviews are scheduled to occur throughout the study. The purpose of these IAD reviews is to examine the safety data and guide dose selections.

In Part A, the investigator and the Lilly clinical pharmacologist/CRP/study team will make the determination regarding dose escalation based on their review of the safety and tolerability data, along with PK data, as applicable

In Part B, dose selection will be based on PK/PD data.

The investigator will remain blinded and the Lilly clinical pharmacologist/CRP/study team will be unblinded during these IAD reviews.

Additional IAD reviews may be conducted at any time throughout the study, as required, to ensure subjects' safety or to help guide dosing. An assessment committee will not be formed.

6.13. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and "Other" Adverse Events are summarized by treatment group and by MedDRA Preferred Term.

- An adverse event is considered "serious" whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the "Other" category if it is both a TEAE and is not serious. For each SAE and "Other" AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term

  - the number of events experienced.

- Consistent with www.ClinicalTrials.gov requirements, “Other” AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- Adverse event reporting is consistent with other document disclosures (for example, the clinical study report [CSR], manuscripts, and so forth)