Statistical Analysis Plan Version 1 I9H-MC-FFAB

A Phase 1 Randomized, Placebo-Controlled Study to Determine the Effect of LY3316531 on Capsaicin-Induced Dermal Blood Flow in Healthy Male Subjects

NCT03611608

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1. Statistical Analysis Plan: I9H-MC-FFAB: A Phase 1 Randomized, Placebo-Controlled Study to Determine the Effect of LY3316531 on Capsaicin-Induced Dermal Blood Flow in Healthy Male Subjects [from protocol I9H-MC-FFAB]

IL-23/CGRP Bispecific Antibody (LY3316531)

A single site, Phase 1, subject- and investigator- blind, placebo-controlled, parallel-dose group, single-dose study to assess target neutralization of CGRP following a single IV dose of LY3316531 versus placebo in healthy male subjects.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol I9H-MC-FFAB
Phase 1

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3. Revision History

Version	Version Date	Description of Change
SAP Version 1	15 October 2018	

4. Study Objectives

4.1. Primary Objective

To assess target neutralization of calcitonin gene-related peptide (CGRP) following a single intravenous (IV) dose of LY3316531 versus placebo in healthy male subjects via capsaicin-induced dermal blood flow (DBF) as measured using laser Doppler imaging (LDI).

4.2. Secondary Objectives

To assess the safety and tolerability of a single dose of LY3316531 in healthy male subjects.

To characterize the pharmacokinetics of LY3316531 following IV administration in healthy male subjects.

4.3. Exploratory Objectives

To evaluate the formation of antidrug antibody (ADA) to LY3316531.

To evaluate the relationship between LY3316531 exposure and total CGRP plasma levels.

To evaluate the relationship between LY3316531 exposure and capsaicin-induced DBF.

To evaluate the relationship between capsaicin-induced DBF and total CGRP plasma levels.

5. Study Design

5.1. Summary of Study Design

Study I9H-MC-FFAB is a Phase 1 single-site, randomized, subject- and investigator-blind, placebo (Pbo)-controlled, parallel-dose group, single-dose study of LY3316531 (LY) in healthy male subjects. The study will evaluate one cohort (Cohort 1) of 16 subjects (12 LY:4 Pbo) with a planned single dose of 300-mg LY3316531 via intravenous (IV) administration. Should an effect not be observed at this starting dose, an optional cohort (Cohort 2) of 12 subjects (9 LY:3 Pbo) may be evaluated with a dose not to exceed 2000-mg IV or the highest tolerable and safe dose evaluated in the single-ascending dose Study I9H-MC-FFAA. Subjects will be followed for up to 80 days post treatment administration.

5.2. Determination of Sample Size

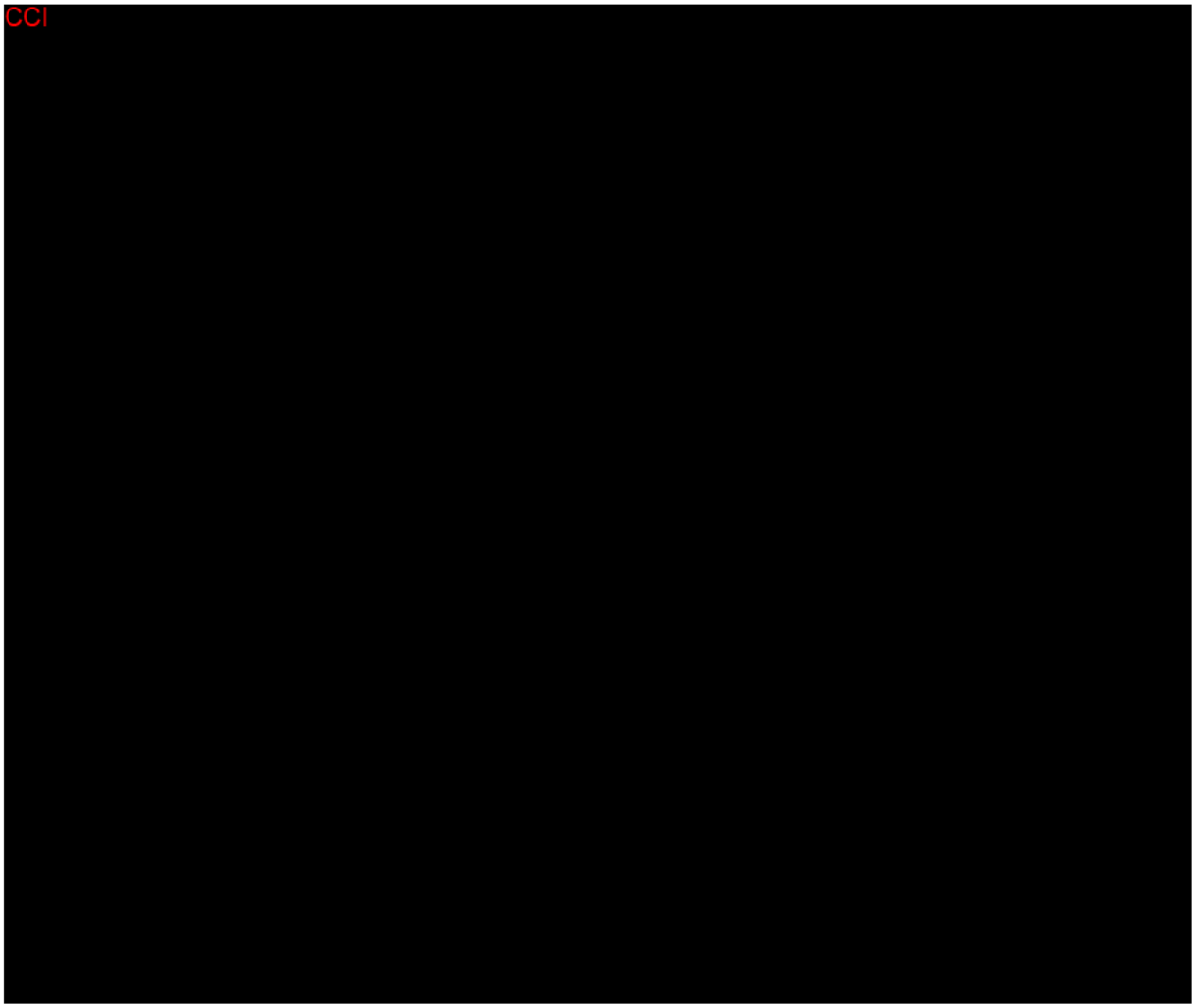
Cohort 1 is planned to enroll 16 subjects (12 LY:4 Pbo). Optional Cohort 2 is planned to enroll 12 subjects (9 LY:3 Pbo). It is not planned to replace subjects; however, subjects may be replaced if necessary to meet study objectives or at the discretion of the Sponsor.

The choice of sample size was based on the statistical power to meet the primary endpoint for a single cohort. CCI [redacted]

CCI [redacted] A two-sample t-test with unpooled variance estimates (using Satterthwaite's approximation to the degrees of freedom) is used to compute the power CCI [redacted]

Under the assumptions stated above, Study FFAB has greater than 80% power CCI [redacted]

CCI



CCI

5.3. Method of Assignment to Treatment

Randomization tables for allocation of LY3316531 or Pbo will be prepared by the statistician or designee for the study and provided to the site pharmacists involved in dose preparation.

The allocation and dispensation of the IP will be fully documented and verified by a second person. Detailed records of the amounts of the IP received, dispensed, and remained at the end of the study will be maintained by the site pharmacy.

6. A Priori Statistical Methods

6.1. General Considerations

Data analyses will be provided by treatment groups and for all study subjects combined wherever appropriate. For continuous variables, summary statistics will include number of subjects, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of subjects, frequency, and percentages. The interpretation of the study results will be the responsibility of the investigator with the pharmacokineticist and statistician. Summary tables, data listings and graphs will be produced with SAS version 9.4, and R version 3.5 or newer will be used for inferential and exploratory analyses. Other software, such as Spotfire, may be used as appropriate to aid the team in decision-making, at the discretion of the statistician and statistical analyst.

Treatment groups will be defined as the LY3316531 dose or placebo. The placebo group will include placebo subjects from all cohorts, if applicable.

Unless otherwise specified, baseline will refer to value collected at the baseline time point. This is usually the value prior to first dosing occasion within the dosing period. In case a specific baseline value is missing, the value at the nearest time point will be used, provided that it is before first dosing. If there are no measurements before dosing then the baseline will be missing.

Unless otherwise specified, missing data will not be imputed and kept missing in the data analyses.

Pharmacokinetic/Pharmacodynamic analyses will be conducted on data from all subjects who receive a dose of LY3316531 and have evaluable PK, total CGRP, or LDI data.

Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

All protocol deviations that occur during the study will be considered for their severity and impact, and will be taken into consideration when subjects are assigned to analysis populations prior to database lock and unblinding. Details of subject assignment to the analysis populations will be listed.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post hoc analyses and incomplete disclosures of analyses.

6.2. Subject Disposition

All subjects 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. A disposition table for all enrolled subjects will be provided.

6.3. Subject Characteristics

The subject's age, sex, weight, height, racial designation, or other demographic and study disease characteristics will be recorded and summarized, and may be used in the pharmacokinetic, pharmacodynamics, and safety analyses as quantitative or classification variables.

6.4. Treatment Compliance

The IP will be administered at the clinical site, and documentation of treatment administration will occur at the site. No analysis for treatment compliance will be performed.

6.5. Concomitant Therapy

In the event medication is used, the name of the drug, the dose and the dosage regimen will be recorded in the CRF. Concomitant therapies will be listed.

6.6. Primary Outcome and Methodology

The primary study objective is to assess target neutralization of CGRP following a single IV dose of LY3316531 versus placebo in healthy subjects via capsaicin-induced DBF as measured using LDI.

The primary objective is measured as decrease from baseline within 30 days, relative to placebo, in capsaicin-induced DBF (by blocking CGRP) following at least 1 dose level of a single IV dose of LY3316531. The primary objective is framed as the alternative hypothesis H_a of the hypothesis-testing construct,

$$H_0: \mu_{LY} = \mu_{Pbo} \text{ versus } H_a: \mu_{LY} > \mu_{Pbo}$$

where μ_{LY} and μ_{Pbo} represent the true mean reduction from baseline in capsaicin-induced DBF.

Statistical significance will be assessed using one-sided, two-sample t-tests with significance established with a p-value less than 0.10. The test statistic, t, is the Behrens-Welch test statistic evaluated as a Student t quantile with degrees of freedom using Satterthwaite's approximation, and has the form,

$$t = \frac{\bar{y}_{LY} - \bar{y}_{Pbo}}{\sqrt{\frac{s_{LY}^2}{n_{LY}} + \frac{s_{Pbo}^2}{n_{Pbo}}}}$$

where n_i is the sample size and

$$s_i^2 = \frac{\sum_{j=1}^{n_i} \left(y_{ij} - \bar{y}_i\right)^2}{n_i - 1}$$

is the sample variance for treatment group $i = LY, Pbo$.

It may not be reasonable to assume the treatment groups have similar variance, therefore Satterthwaite's approximation will be used to approximate the degrees of freedom, which is given by

$$df = \frac{\left[\frac{s^2_{LY}}{n_{LY}} + \frac{s^2_{Pbo}}{n_{Pbo}}\right]^2}{\frac{\left(s^2_{LY}/n_{LY}\right)^2}{n_{LY}-1} + \frac{\left(s^2_{Pbo}/n_{Pbo}\right)^2}{n_{Pbo}-1}}.$$

The test statistic will be computed for Visits 3 and 4 (post-baseline visits within 30 days of dosing). No correction for multiplicity will be applied, as is customary in Phase 1 trials.

In the event additional cohorts are recruited, subjects assigned to similar treatment arms will be pooled to assess the primary analysis. This includes subjects who are assigned to placebo, and (if applicable) subjects who are assigned to the same LY dosage.

6.7. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

All PK and PK/PD analyses will be performed by Lilly Global PK/PD/PMx. Details will be included in a separate analysis plan and/or described in the clinical study report (CSR).

6.8. Safety Analyses

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and ECG parameters. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data. Baseline for safety parameters will be defined as the last evaluable value before the first dose for each subject.

6.8.1. Adverse Events

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

The discontinuations due to adverse events will be listed. The serious adverse events (SAEs), the severe treatment emergent adverse events (TEAEs), the adverse events occurring on or after signing study informed consent document and the pre-existing conditions will be listed.

Adverse events reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity after enrollment which will be classified as TEAEs. The incidence of TEAEs for each treatment group and total LY will be presented by system organ class (SOC) and preferred term (PT), by severity and by association with investigational product as perceived by the investigator. A table will present the frequency of subjects with TEAEs by Week. The frequency of subjects with TEAEs will be presented by treatment group, by preferred term. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

6.8.2. Clinical Laboratory Evaluation

The safety laboratory parameters will be listed and summarized using standard descriptive statistics per treatment group.

6.8.3. Vital Signs and Other Physical Findings

Vital signs including pulse rate, SBP, DBP and body temperature will be listed. There will be a table summarizing vital sign parameters (pulse rate, SBP, DBP) by treatment group and by time. A table presenting the mean change from baseline supine vital sign parameters (pulse rate, SBP, DBP) by treatment group for each of these time points: Day 1 (including predose, end of infusion, and 2, 6, and 12 hours after start of infusion), Day 2 (24 hours after start of infusion), and Days 10, 24, 38, 52, 66 and 80 will be presented. The table may be split in to multiple tables, by time, if necessary to easily view the data.

6.8.4. Electrocardiograms

ECG parameters will be listed and summarized by treatment group and time. Mean changes from baseline for QT and QTcF parameters will be summarized by treatment group and by time (Day 1: predose, end of infusion, and 6 hours after start of infusion; and Day 2: 24 hours after start of infusion). A table of frequency of QT and QTcF >500msec at any time point will be provided by treatment group. A table of frequency of mean change from baseline of QT and QTcF >60msec at any time will be presented by treatment group. A Graph of mean changes from baseline QT and QTcF versus time by treatment group and a graph of mean changes from baseline QT and QTcF versus LY3316531 concentration by time will be provided.

6.9. Interim Analyses and Data Monitoring

A single interim analysis that includes all safety and LDI data, and may include PK data, through 23 days post dose (Day 24) will inform the decision to proceed to Phase 2. The interim analysis will be based on the highest dose level evaluated (either Cohort 1 or optional Cohort 2, if implemented).

Note that the primary objective will have complete data at the time of the interim analysis, and therefore the analysis will be the same as described in the above sections. Safety analyses will also be unchanged at interim, but all safety visits may not be complete at the time the interim occurs. All available data will be summarized as described in the sections above.

The decision whether or not to add an additional patient cohort may be made as early as 9 LY and 3 Pbo subjects with Visit 3 data, however it is planned that all subjects will have completed Visit 4 (same as the timing for the interim analysis). The analyses will be the same as described in Section 6.6.

6.10. Planned Exploratory Analyses

In the event that an additional cohort is chosen (Cohort 2), and the dose of LY to be administered is the same across cohorts, an analysis of the primary endpoint with pooled responses across cohorts for subjects randomized to the same treatment group (placebo, 300mg LY) will be

performed. If the protocol allows for the pooled analysis, this will be part of the primary (see Section 6.6 for full details).

Other exploratory analyses will be performed by PK/PD and LEM functions.

6.11. 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 adverse events, 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, 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 Serious AE 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).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

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