Statistical Analysis Plan J2J-MC-JZLB (1)

# EMBER-2: A Phase 1, Open-Label, Preoperative Window Study Evaluating the Biological Effects of LY3484356 in Post-menopausal Women with Stage I-III Estrogen Receptor-Positive, HER2-Negative Breast Cancer

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# 1. Statistical Analysis Plan: J2J-MC-JZLB: EMBER-2: A Phase 1, Open-Label, Preoperative Window Study Evaluating the Biological Effects of LY3484356 in Post-menopausal Women with Stage I-III Estrogen Receptor-Positive, HER2-Negative Breast Cancer



LY3484356 Breast Cancer

This is a Phase 1 open-label, randomized pre-operative window study in post-menopausal women with Stage I to Stage III ER+ and HER2- breast cancer to assess pharmacodynamics, pharmacokinetics, biological effects and safety of SERD LY3484356.


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[Protocol J2J-MC-JZLB]
[Phase 1]

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

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# 2. Table of Contents

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# 3. Revision History

SAP Version 1 was approved prior to the first visit when a subject receives study drug or any other protocol intervention.

# 4. Study Objectives

| Objectives | Endpoints |
|---|---|
| Primary | |
| • Determine PD effect of each dose level of LY3484356 on ER expression, in patients with ER+ early stage breast cancer. | • Change in ER expression (as measured by IHC and quantified by H-score) between pre- and on-treatment tumor samples, at each dose level of LY3484356 |
| Secondary | |
| • Assess PD effect of each dose level of LY3484356 on Tumor cell proliferation. | • Change in Ki-67 index (as measured by IHC and expressed by % positive scoring) between pre- and on-treatment tumor samples, at each dose level of LY3484356 |
| • Assess PD effect of each dose level of LY3484356 on PR expression. | • Change in PR expression (as measured by IHC and quantified by H score) between pre- and on-treatment tumor samples, at each dose level of LY3484356 |
| • Evaluate safety and tolerability of each dose level of LY3484356. | • Incidence of investigator assessed AEs per NCI CTCAE v5.0, at each dose level of LY3484356 |
| • Evaluate PK effect of each dose level of LY3484356. | • Plasma concentrations of LY3484356, at each dose level of LY3484356 |
| Exploratory | |
| CCI | |

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ER = estrogen receptor; IHC = immunohistochemistry; NCI = National Cancer Institute; PD = pharmacodynamics; PK = pharmacokinetic; PR = progesterone receptor.

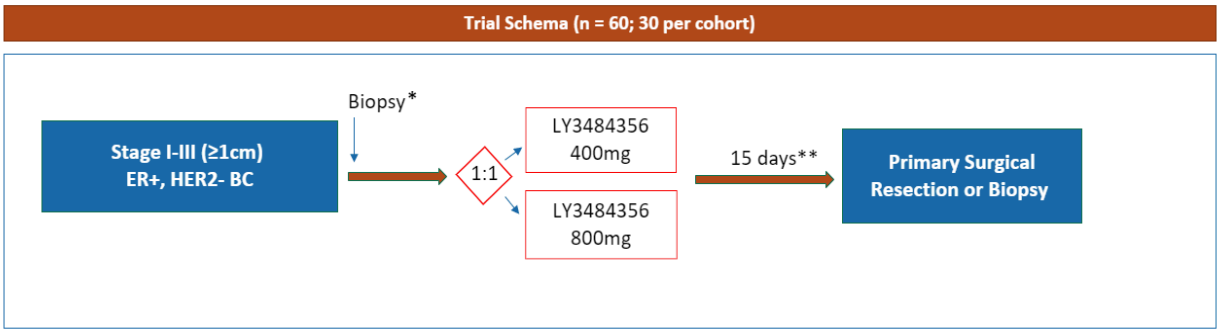
# 5. Study Design

## 5.1. Summary of Study Design

Study EMBER-2 is a Phase 1, open-label, randomized, pre-operative window study of LY3484356 in post-menopausal women with Stage I to III ER+, HER2- breast cancer who are scheduled for surgery with curative intent. Patients will consent to provide tumor samples obtained at the time of diagnosis and at the time of scheduled surgery or repeat biopsy, for the purpose of biomarker analyses. Patients will then be randomized to one of the dose levels of LY3484356 and receive LY3484356 for 15 days, up to and including the day of scheduled surgery or repeat biopsy (if neoadjuvant therapy is subsequently planned). Tumor samples taken pre- and on-treatment with LY3484356, at the time of diagnosis and scheduled surgery/repeat biopsy, respectively, will then be evaluated for biologic effects, as outlined in the study objectives.

A treatment window of 15 days (-2 to +7 days [ie, a range of 13 to 22 days of LY3484356 treatment]) will be permissible to facilitate flexibility in scheduling of the on-treatment surgery/biopsy. The last dose of LY3484356 will be taken on the morning of surgery/biopsy.

The study schema is illustrated below:




Abbreviations: BC = breast cancer; ER+ = estrogen receptor positive; HER2- = human epidermal growth factor receptor 2 negative.

* Baseline (pre-treatment) tumor tissue collection:

- Adequate archival tissue from diagnostic biopsy is acceptable if collected within 6 weeks prior to consent.
- Fresh biopsy:
  - Required if archival tissue is unavailable/exhausted or was collected >6 weeks prior to consent or while the patient was taking Hormone Replacement Therapy
  - Optional for the purpose of Oncotype DX testing

** Allowable treatment window to facilitate scheduling of on-treatment surgery/biopsy: 15 days (- 2 to + 7 days [ie, a range of 13 to 22 days of LY3484356 treatment will be permissible.])

## 5.2. Determination of Sample Size

Approximately [redacted] participants will be assigned equally to the different dose-level cohorts in this study to ensure that conservatively 20 participants, with evaluable biomarker data are ultimately

available for analysis from each cohort. The sponsor may elect to continue accrual until sufficient biomarker data is generated.

The sample size of 20 participants per cohort provides a 90% tolerance probability that the 2-sided 90% confidence interval (CI) for geometric mean of change from baseline in ER expression for each cohort will extend no more than 0.34 from the observed geometric mean in logarithm scale, assuming that the true standard deviation is 0.74 (Kuter et al. 2012) and that the CI is based on the t statistic.

## 5.3. Method of Assignment to Treatment

Participants will be randomized to one of the dose levels of LY3484356. Randomization will be stratified by tumor histology (infiltrating ductal carcinoma [IDC] versus infiltrating lobular carcinoma [ILC]; as locally determined from the diagnostic tumor biopsy).

# 6. A Priori Statistical Methods

## 6.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee.

All confidence intervals (CIs) will be given at a 2-sided 95% level, unless otherwise stated.

Log normally distributed variables were log transformed before analysis and summaries reported on the original (anti-log) scale.

Unless otherwise noted, summaries of continuous variables will include a mean, median, standard deviation, minimum, and maximum.

Unless otherwise noted, summaries of categorical variables will include the frequency and percentage (relative to the population being analyzed) of each category.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

### *6.1.1. Populations*

The following analysis populations will be defined for this study:

**Intention-to-Treat (ITT) population**: will include all enrolled/randomized participants. The ITT analysis will consider allocation of participants to treatment groups as assigned/randomized and not by actual treatment received. This analysis set will be used for all baseline analysis.

**Safety population:** will include all enrolled/randomized participants who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the first dose of study treatment a participant actually received, regardless of the participant's cohort assignment. The safety analysis set will be used for all dosing/exposure and safety analyses.

**Biomarker evaluable (BE) population:** will include the subset of participants from the ITT from whom valid baseline and post-treatment result have been obtained. Different biomarker evaluable populations need to be defined for different biomarkers.

### *6.1.2. Definitions and Conventions*

**Study treatment** refers to LY3484356.

The **date of randomization** is the date the patient was randomly assigned to a study treatment using the IWRS.

The **date of first dose** is the date of the first dose of LY3484356.

The **baseline value of a safety assessment** is the last value observed prior to the first dose of LY3484356.

The **baseline value of an efficacy assessment** is the last value observed prior to the date of enrollment/randomization. If a patient's first assessment occurs after enrollment/randomization but prior to the first dose, this assessment will be used as the baseline.

The **study day of a safety event or assessment** will be calculated as:

- the difference between the date of the event or assessment and the date of first dose plus 1 for all events or assessments occurring on or after the day of first dose. For example, if an event occurs on 08MAR2016 and the date of first dose was 06MAR2016, the study day of the event is 3.
- the difference between the date of the event or assessment and the date of first dose for all events or assessments occurring before the day of first dose. For example, if an event occurs on 05MAR2016 and the date of first dose was 06MAR2016, the study day of the event is -1.

The **study day of an efficacy event or assessment** will be calculated as:

- the difference between the date of the event or assessment and the date of enrollment/randomization plus 1 for all events or assessments occurring on or after the date of randomization.
- the difference between the date of the event or assessment and the date of enrollment/randomization for all events or assessments occurring before the date of randomization.

One **month** is defined as 365/12 days.

Unless otherwise noted, summaries of continuous variables will include a mean, median, standard deviation, minimum, and maximum.

Unless otherwise noted, summaries of categorical variables will include the frequency and percentage (relative to the population being analyzed) of each category.

## 6.2. Adjustments for Covariates

The stratification factor used in randomization is considered important prognostic factors and are thought to be associated with outcomes. Subgroup analyses based on the stratification factor will be conducted if appropriate.

## 6.3. Handling of Dropouts or Missing Data

With the exception of dates, missing data will not be imputed.

## 6.4. Participant Disposition

A detailed description of participant disposition based on all entered participants (participants who have signed the informed consent) will be provided. It will include a summary of the number and percentage of participants entered into the study, rescreened after screen failure, enrolled/randomized in the study, and treated in the study, reasons for discontinuation from study treatment (safety population only), and reasons for discontinuation from study (ITT population only). Reason for discontinuation from both the study treatment and the study will be summarized by pre-determined categories.

## 6.5. Participant Characteristics

### *6.5.1. Demographics*

Participant demographics will be summarized. Participant demographics will include age, race, ethnicity, height, weight, and body mass index.

### *6.5.2. Baseline Disease Characteristics*

Disease characteristics will be summarized. Disease characteristics will include the following:

- Initial pathological diagnosis
- Disease stage (Stage IIA, Stage IIB, etc.) at study entry
- Histopathological diagnosis grade (G1, G2, etc.) at study entry
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS)
- HER2 status (negative/positive)
- Progesterone receptor status (negative/positive)
- Estrogen receptor status (negative/positive)
- Baseline ER expression, Ki-67 index, and PR expression

### *6.5.3. Historical Illnesses/Pre-existing Conditions*

Historical illnesses and pre-existing conditions (using Preferred Term(s) [PTs] from the most current version of the Medical Dictionary for Regulatory Activities [MedDRA®]) will be summarized.

## 6.6. Treatment Compliance

Treatment compliance information for all oral study drugs will be collected through pill counts. Compliance will be calculated as the ratio of total dose taken to the total assigned dose (minus any dose adjustments and doses omitted/withheld for medical or logistical reasons).

## 6.7. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization drug dictionary. All concomitant medications will be summarized by number and percentage of participants for the safety population using the base name (without esters or salts).

## 6.8. Primary and Secondary Biomarker Analyses

The primary and secondary biomarker analyses will be performed based on the BE population for each biomarker.

**Change in ER expression** is defined as the change from the pre-treatment to on-treatment sample. The geometric mean of change in the ER H-score, the percent change in H-score of ER expression, and the 90% CI (based on t statistic) will be summarized for each cohort.

**Change in Ki-67 index** is defined as the change from the pre-treatment to on-treatment. The geometric mean of change in Ki-67 expressing positive cells, the percent change in Ki-67 expressing positive cells, and its 90% CI (based on t statistic) will be summarized for each cohort. Subgroup analyses will be performed in participants with higher (>5%) baseline Ki-67%.

**Change in PR expression** is defined as the change from the pre-treatment to on-treatment. The geometric mean of change in the PR H-score, the percent change in H-score of PR expression, and the 90% CI (based on t statistic) will be summarized for each cohort.

Primary analysis of these variables (i.e. change from baseline for each biomarker) will utilize a linear model with arm and tumor histology as covariates, as below:

$$Y_{ijk} = \mu + \alpha_i + \beta_j + \varepsilon_{ijk}$$

where $Y_{ijk}$ is the log ratio of each biomarker value at the on-treatment time point to the value at the pre-treatment time point for patient $k$ in arm $i$ with tumor histology status $j$. Least square mean (LSM) estimates and standard errors for each arm will be derived from this model.

LSM estimates and CIs will need to be back transformed to the geometric mean scale. Letting $\hat{\mu}$ denote LSM estimate, the geometric mean change and geometric mean percent change will be calculated as $\exp(\hat{\mu})$ and $100\%(\exp(\hat{\mu})-1)$, respectively.

For each of the biomarkers above, not only the geometric mean change from baseline and percent change will be reported, the medians, ranges and geometric means for the pre-treatment and on-treatment results will also be reported. A plot of change in the biomarker values will also be provided.

Subgroup analysis for each of the biomarker endpoints by the stratification factor (i.e. tumor histology) may also be conducted if deemed appropriate.

## 6.9. Safety Analyses

### *6.9.1. Extent of Exposure*

Drug exposure and dose intensity for LY3484356 will be summarized. Drug exposure will include summaries of duration on therapy (in weeks), and cumulative dose. Dose intensity will be calculated as the actual cumulative amount of drug taken divided by the duration of treatment. Relative dose intensity will be calculated as the actual amount of drug taken divided by the amount of drug prescribed times 100% (expressed as a percentage).

### *6.9.2. Adverse Events*

Adverse event (AE) severity grades will be assigned by the investigator using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. In addition, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within MedDRA.

Preexisting conditions are defined as AEs that either are ongoing at informed consent and or end on or after informed consent. Pre-existing conditions will be included in the listing of AE so that the history of AEs can be traced.

A treatment-emergent adverse event (TEAE) is defined as an AE that first occur or worsen in CTCAE grade after the first dose of study treatment. The MedDRA LLT will be used in the treatment-emergent computation.

The following summaries and listings will be produced:

- Overview of adverse events
- Summary of TEAEs by preferred term (PT) (any grade and Grade ≥ 3)
- Summary of Serious AEs by PT
- Summary of AEs as reason for study treatment discontinuation by PT
- Summary of AEs as reason for surgery delay by PT
- Listing of AEs
- Summary of DLT-equivalent Toxicities
- Listing of DLT-equivalent Toxicities

The TEAE and SAE summaries will be produced for all TEAEs/SAEs and repeated for TEAEs/SAEs related to study treatment, where relationship of the AE to the study treatment will be assessed by the investigator (yes or no).

### *6.9.3. Deaths and Other Serious Adverse Events*

A summary of all deaths, including reasons for deaths, will be provided. All deaths, deaths on study treatment, deaths within 30 days of discontinuation of study treatment, deaths on study treatment or within 30 days of discontinuation of study treatment, and deaths after 30 days of discontinuation of study treatment will be summarized by reason for death. For deaths due to AE, the preferred term will be provided. In addition to the tabular summary, a by-participant listing of all deaths on study not attributed to study disease by the investigator will be provided.

### *6.9.4. Clinical Laboratory Evaluation*

All relevant hematology and chemistry laboratory values will be graded according to CTCAE Version 5. Shift tables showing the change from baseline to the worst grade on study will be summarized. Abnormal laboratory parameters will be listed.

### *6.9.5. Vital Signs and Other Physical Findings*

All vital signs (e.g. temperature, blood pressure, pulse rate, height, weight) will be summarized. A summary of change from baseline in vital sign parameters will also be provided.

### *6.9.6. Electrocardiograms*

A summary of single local electrocardiograms (ECGs) will be provided. The summary will classify participants as having normal or abnormal. Adverse events that could be associated with abnormal ECGs will be presented, if appropriate.

## 6.10. Important Protocol Deviations

Important protocol deviations that potentially compromise the data integrity and participants' safety will be summarized. These deviations will include deviations that can be identified programmatically and those which can only be identified by the clinical research associates during monitoring. Important protocol deviations are described in another document within the study Trial Master File.

## 6.11. Interim Analyses

No interim analyses are planned for this study. However, each cohort will be continuously monitored for safety. Enrollment to a cohort will be temporarily halted and a safety data review will be triggered if the posterior Pr (DLT rate or the rate of AEs that result in delay in surgery is >20%)≥50% (i.e., observed cumulative incidence ≥20%) using a beta-binomial Bayesian model with a prior Beta (0.5,0.5). A cohort may be closed early and a re-evaluation of dose may occur based upon the safety data review.

The operating characteristics including the probability of potential early stopping, and the probability of declaring excessive toxicity at the end of the trial are summarized in the table below. CCI


## 6.12. Planned Exploratory Analyses

Changes in other tumor-related biomarkers may be performed. Other exploratory analyses not specified in the SAP may be performed as deemed appropriate.

## 6.13. Pharmacokinetic/Pharmacodynamic Analyses

The analyses and methods will be described in a separate document.

## 6.14. 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 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.

In addition, the following rules apply in order to meet the requirement for participant flow and accurately represent study completion.

| **Study discontinuation reason** | **Completed** | **Not Completed** |
|---|---|---|
| Participants who have completed all on-treatment visits | X | |
| Death due to any cause* | | X |
| Lost to follow-up* | | X |
| Withdrew consent to study participant (patient or physician)* | | X |
| Discontinued due to adverse events | | X |

*Include participants only if not meeting the definition for "Completed".

# 7. References

Kuter I, Gee JMW, Hegg R, et al. Dose-dependent change in biomarkers during neoadjuvant endocrine therapy with fulvestrant: results from NEWEST, a randomized Phase II study. *Breast Cancer Res Treat.* 2012;133(1):237-246. https://doi.org/10.1007/s10549-011-1947-7

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**Signature meaning: Approved**