Statistical Analysis Plan for I3Y-MC-JPCP

An Open-Label, Randomized Phase 2 Study of the Impact of Food on Tolerability when Receiving Abemaciclib for Patients with Previously Treated Hormone Receptor-Positive, HER2-Negative, Metastatic Breast Cancer

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Abemaciclib (LY2835219)

Open-Label, Randomized Phase 2 Study of the Impact of Food on Tolerability when Receiving Abemaciclib for Patients with Previously Treated Hormone Receptor-Positive, HER2-Negative, Metastatic Breast Cancer

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Protocol I3Y-MC-JPCP
[Phase 2]

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

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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

4.1. Primary Objective

The primary objective of the study is evaluate and summarize incidence of severe diarrhea (≥Grade 3) or prolonged Grade 2 diarrhea (defined as >7 days duration), including the incidence of dose reductions, dose interruptions, and/or treatment discontinuations due to severe diarrhea or prolonged Grade 2 diarrhea over the first 3 cycles when abemaciclib is administered:

- with a meal
- without a meal, taken in the modified fasted condition
- without regard to food

The endpoints for the primary objective include:

- Incidence of severe diarrhea (≥Grade 3)
- Incidence of prolonged Grade 2 diarrhea (defined as >7 days duration)
- Dose reductions due to diarrhea
- Dose interruptions due to diarrhea
- Treatment discontinuations due to diarrhea
- Utilization of antidiarrheals

4.2. Secondary Objectives

The secondary objectives of the study are:

- To assess safety and toxicity profile of abemaciclib (i.e. to evaluate overall safety incidence and severity of TEAEs, SAEs, deaths, and clinical laboratory abnormalities)
- To evaluate the PK parameters of abemaciclib and its metabolites (i.e. to evaluate Steady-state concentrations of abemaciclib and its metabolites LSN2839567 and LSN3106726)

5. A Priori Statistical Methods

5.1. Sample Size Determination

The primary objective of this study is to evaluate the impact of 3 different meal settings on the incidence of severe diarrhea (≥Grade 3) or prolonged Grade 2 diarrhea (>7 days duration) as well as dose reductions, dose interruptions, and treatment discontinuations due to diarrhea, and utilization of antidiarrheals for patients receiving abemaciclib monotherapy. This study will enroll up to approximately 100 patients to obtain approximately 20 patients who complete the primary outcome phase per meal administration condition. Randomization will be 1:1:1 to the 3 administration conditions and randomization will be stratified by region. The region is defined as: AMERIT (Russia, Ukraine, Turkey) vs Non-AMERIT (Belgium, Spain, Australia). The sample size is based on regulatory guidance, not statistical powering.

5.2. General Considerations

5.2.1. Populations

The following analysis sets will be defined for this study:

Intention-to-treat (ITT) analysis set: will include all randomized patients. The ITT analysis of efficacy data will consider allocation of patients to treatment groups as randomized and not by actual treatment received. This analysis set will be used for all baseline analyses and patient dispositions.

Per-protocol (PP) analysis set: will include all randomized patients who receive at least 1 dose of abemaciclib and do not have any major protocol violations that could potentially affect the conclusions of the study, such as significant noncompliance with meal administration conditions or abemaciclib treatment administration. This analysis set will be used for sensitivity analyses related to the primary objective.

For study Arm 1 (take abemaciclib with meal) and Arm 2 (take abemaciclib without meal), the PP analysis set will include all randomized patients who receive at least 1 dose of abemaciclib and who are at least 75% compliant with meal administration conditions and abemaciclib treatment administration.

For study Arm 3 (take abemaciclib without regard to food), the PP analysis set will include all randomized patients who receive at least 1 dose of abemaciclib and who are at least 75% compliant with abemaciclib administration.

Safety analysis set: will include all randomized patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the cohort assignment. The safety analysis set will be used for analyses related to the primary objective and for all dosing/exposure and safety analyses.

Pharmacokinetic analysis set: will include all enrolled patients who received at least 1 dose of abemaciclib and have at least 1 postbaseline evaluable PK sample and evaluable dosing information.

5.2.2. Definitions and Conventions

Study drug or **study treatment** refers to abemaciclib.

The date of first dose is the date of the first dose of study drug.

The **baseline value of a safety/efficacy assessment** is the last value observed prior to the first dose of study drug.

The **study day of a safety/efficacy 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 08JUN2014 and the date of first dose was 06JUN2014, 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 05JUN2014 and the date of first dose was 06JUN2014, the study day of the event is -1.

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.

5.2.3. Handling of Dropouts and Missing Data

General rules for imputing dates related to AE or concomitant therapy:

- Onset date of an AE or start date of a concomitant therapy:
  - If only the day is missing, the date will be set to:
    - First day of the month that the event occurred, if the onset yyyy-mm is after the yyyy-mm of first study treatment.
    - The day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of the first study treatment.
  - If both the day and month are missing, the complete date will be set to:
    - January 1 of the year of onset, if the onset year is after the year of the first study treatment.
    - The date of the first dose, if the onset year is the same as the year of the first study treatment.
- Resolution date of an AE or end date of a concomitant therapy:

- If only the day is missing, the date will be set to the last day of the month of the occurrence, or to the date of death if the patient died in the same month.
- If both the day and month are missing, the date will be set to 31 December of the year of occurrence.

If a date is completely missing, then the AE will be considered treatment-emergent. In case of additional therapies, the therapy will be considered concomitant.

General rule for imputing other dates: If a date variable is needed for an analysis, use the following general rule to impute incomplete date:

- If the date has no missing year and month but the day is missing, then assign Day 1 to the day
- If the date has no missing year, but has missing month, then assign January to the month.

However, after imputation, check if the imputed date is logically consistent with other relevant date variable(s) and make appropriate correction if necessary. For example, if a visit start date was 10 May 2015 and a tumor assessment date was xx May 2015 (missing day) but it was known that it occurred after that visit, then after imputation, the tumor assessment date became 01 May 2015. In this case, the imputed tumor assessment date should be compared to the visit start date and then corrected to be the visit start date, 10 May 2015.

Safety analysis: The following rule for missing data processing will apply for safety analysis:

- Missing classifications concerning study medication relationship will be considered as related to study medication (both components).
- If the AE onset date is missing or partial, the date will be compared as far as possible with the date of first dose of study medication when determining whether or not the AE is present at baseline. In this case, the AE will be assumed to be treatment emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first dose of study medication.

5.3. Patient Disposition

A detailed description of patient disposition will be provided, including a summary of the number and percentage of patients randomized, treated, as well as number and percentage of patients completing the study or discontinuing the study (by study arms/overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

5.4. Demographics and Baseline Characteristics

5.4.1. Demographics

Demographic characteristics will be summarized by study arms using descriptive statistics for randomized as well as for treated patients by race, ethnicity, age, age groups (<65 years, ≥65

years), height, weight, body mass index (BMI), country and region (AMERIT vs Non-AMERIT).

5.4.2. Disease Characteristics

Disease characteristics will be summarized by study arms using descriptive statistics for randomized as well as for treated patients. Disease characteristics will include the following: disease diagnosis, basis for diagnosis, and disease stage. In addition, the disease charateristics will include duration of disease (initial diagnosis to date of first dose), baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS), HER2 status, Progesterone Receptor (PR) status and Estrogen Receptor (ER) status.

5.4.3. Historical Illnesses and Prior Therapies

Historical illnesses are events in the past that ended before the date informed consent is signed. Historical illnesses (coded according to the Medical Dictionary for Regulatory Activities [MedDRA]) will be listed for all treated patients.

Prior therapies, including systemic therapy, radiotherapy and surgeries will be listed for all randomized patients. Prior radiotherapy and systemic therapy will be summarized by the number of patients with at least one of each type of treatment, as well as by reason for regimen (e.g., palliative, curative, etc.). Additionally, the number of regimens of prior systemic therapy and (where available) the reason for prior regimens will be summarized.

5.4.4. Concomitant Therapy

Concomitant medications will be summarized by study arms and listed for the safety population.

5.5. Treatment Compliance

Treatment compliance information for study drug will be collected through capsule counts at each visit. The estimate of percent abemaciclib treatment compliance will be given by:

$$\text{Percent Treatment Compliance} = \frac{\text{actual cumulative dose taken}}{\text{expected cumulative dose to be taken}} \text{ x } 100$$

The actual cumulative dose taken will be determined based on counting the number of capsules returned at each visit and subtracting that number from the number of capsules dispensed over the course of the first 3 cycles. The expected cumulative dose to be taken will be determined based on the assigned dose and taking into account any dose reductions or omissions.

Compliance to the administration condition for Arm 1 and Arm 2 will be assessed as the proportion of doses during the first 3 cycles of treatment that are taken during the meal window allowed by the assigned administration condition.

The allowed meal window for Arm 1 (taken with a meal) would be taking abemaciclib during a meal or within 30 minutes of end of meal.

The allowed meal window for Arm 2 (taken without a meal) would be taking abemaciclib greater than 60 minutes before start of meal or taking abemaciclib greater than 120 minutes after end of meal.

There is no window for Arm 3 as the abemaciclib is taken without regard to food.

For each dose of abemaciclib taken during the first 3 cycles, the patient will record the administration condition in a diary. The compliance to the administration condition will be based on the available data obtained from diary.

Compliance with Morning Dose Diary, Evening Dose Diary and Bowel Movements Diary will be calculated as the proportion of the actual number of diaries and expected number of diaries.

In addition, timing of dose administration condition with respect to food intake timing may be summarized by study arms for morning and evening dose separately based on ediary.

5.6. Post-discontinuation Therapy

The numbers and percentages of patients reporting post-discontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug name.

5.7. Efficacy Analysis

Efficacy assessments are not applicable in this study. However, the investigator is required to confirm that the patient is still deriving benefit from study treatment and has no evidence of disease progression.

5.8. Analysis Related to Primary Objective

The primary objective of the study includes the evaluation of the following endpoints over the first 3 cycles (primary outcome phase):

- Incidence of severe diarrhea (≥Grade 3)
- Incidence of prolonged Grade 2 diarrhea (defined as >7 days duration)
- Dose reductions due to diarrhea
- Dose interruptions due to diarrhea
- Treatment discontinuations due to diarrhea
- Utilization of antidiarrheals

Analyses for each of these endpoints related to the primary objective will be summarized by treatment arm using safety analysis set population. For descriptive purpose, the odds ratios with 95% confidence intervals along with exact p-value using Fisher's Exact test will be produced for comparing arms with each other. In addition, incidence of severe diarrhea (≥Grade 3) and incidence of prolonged Grade 2 diarrhea (defined as >7 days duration) will be combined into one endpoint. Dose reductions due to diarrhea, Dose interruptions due to diarrhea and Treatment discontinuations due to diarrhea will be combined into another combined endpoint. These two

combined endpoints will be summarized and analyzed using the same approach mentioned above.

The analysess for each of the endpoints related to the primary objective will be repeated using per-protocol analysis set population as a sensitivity analysis.

5.9. Safety Analysis

5.9.1. Extent of Exposure

All patients who receive at least 1 dose of abemaciclib (i.e. the safety analysis set population) will be evaluated for safety and toxicity and exposure.

For abemaciclib, extent of exposure will be measured by pill counts and summarized by cumulatively. The summary will include the total dosages taken and dose intensities. Dose intensity will be calculated as the ratio of total dose taken to the assigned cumulative dose. The assigned cumulative dose for each patient during each cycle is 150 mg per dose × 2 doses per day × 21 days = 6300 mg. The assigned cumulative dose while in this study is 150 mg per dose × 2 doses per day × number of days on treatment.

The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by treatment arm based on data from the first 3 cycles as well as based on data from entire treatment period (i.e. first 3 cycles plus extension phase) separately.

5.9.2. Adverse Events

All patients who receive at least 1 dose of abemaciclib (i.e. the safety analysis set population) will be evaluated for safety and toxicity.

Primary analysis of adverse events will be performed based on data from the first 3 cycles. The secondary analyses of the adverse events will be done based on data from entire study period.

The Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 (or higher) will be used to map reported AEs to MedDRA terms. The MedDRA Lower Level Term (LLT) will be used in the treatment emergent computation. Treatment-emergent adverse events (TEAEs) will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term (PT) within the SOC. Preferred terms identified by Medical as clinically identical or synonymous will be grouped together under a single consolidated PT. For example, 'Neutropenia' and 'Neutrophil count decreased' will be reported as 'Neutropenia'. All listings and summaries will use the PT resulting from this process. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will serve as the reference document for grading the severity of all AEs and other symptoms. Preexisting conditions are defined as AEs that begin prior to the first dose of study drug.

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline.

A serious adverse event (SAE) is any AE during this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition above.

Safety analyses will include summaries of the following by treatment arm:

- treatment-emergent adverse events, including severity and possible relationship to abemaciclib
- serious adverse events, including possible relationship to abemaciclib
- treatment-emergent adverse events leading to dose adjustments
- discontinuations from study treatment due to AEs or death
- Maximum Post Baseline Treatment Emergent CTCAE Lab Toxicities
- treatment-emergent abnormal changes in vital signs.

5.9.3. Deaths

All deaths in this study that are not attributed to study disease by the investigator will be listed along with the reason for death, if known. For those deaths attributed to an AE, the listing will include the PT of the AE. A summary of deaths including reasons for death will be produced.

In addition, a listing of all deaths including those due to study disease along with reason for death (if known) will be produced.

5.9.4. Clinical Laboratory Evaluation

A patient listing of all abnormal laboratory data will be provided with a flag for values outside of the laboratory normal range as well as investigator site, patient identifier, age, gender, race, weight, and visit. Abnormal results will be listed separately for the safety population. In addition, the treatment emergent laboratory events will be summarized in table.

In addition to the investigator-reported AEs, all relevant hematology and chemistry laboratory values will be graded according to CTCAE version 4.0. These derived values will be included on the listings of laboratory data.

5.9.5. Vital Signs, Physical Examinations, and other Observations Related to the Study

All vital signs including blood pressure and heart rate will be listed for all enrolled patients.

5.10. Other Analyses

5.10.1. Pharmacokinetic/Pharmacodynamic Analyses

Abemaciclib PK analyses will be conducted on all patients who have received at least 1 dose of study treatment and have had samples collected (see PK sampling schedule in Appendix 4 of the protocol). Pharmacokinetic (PK) analyses will be performed according to a separate PK/PD analysis plan.

5.10.2. Additional Reports to Support Clinical Trial Registry (CTR) Reporting Results

Analyses provided for the Clinical Trial Registry (CTR) requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs will be summarized by treatment group and by MedDRA PT.
- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE 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 (if certain subjects cannot be at risk for some reason, for example, gender-specific AEs, then the study team must adjust the number to only include the patients at risk)
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, a threshold for frequency of 'Other' AEs can be implemented rather than presenting all 'Other' AEs. For example, 'Other' AEs that occur in fewer than 5% of patients in any treatment group may not be included if a 5% threshold is chosen. The frequency threshold must be less than or equal to the allowed maximum of 5%.
- The completers in the study is defined as the subjects who have completed three cycles of the study treatment.

6. References

National Cancer Institute. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0, DCTD, NCI, NIH, DHHS. 2009.

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