

I3Y-CR-JPBQ Statistical Analysis Plan Version 2

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Compare NSAI (Anastrozole or Letrozole) plus Abemaciclib, a CDK4 and CDK6 Inhibitor, or plus Placebo, and to Compare Fulvestrant plus Abemaciclib or plus Placebo in Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer

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**1. Statistical Analysis Plan:  
I3Y-CR-JPBQ: A Randomized, Double-Blind, Placebo-  
Controlled, Phase 3 Study to Compare NSAI (Anastrozole  
or Letrozole) plus Abemaciclib, a CDK4 and CDK6  
Inhibitor, or plus Placebo, and to Compare Fulvestrant  
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Women with Hormone Receptor-Positive, HER2-Negative  
Locoregionally Recurrent or Metastatic Breast Cancer**

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**Abemaciclib (LY2835219)**

This is a randomized, double-Blind, placebo-controlled, phase 3 study to compare NSAI plus abemaciclib, a CDK4 and CDK6 Inhibitor, or plus placebo, and to compare fulvestrant plus abemaciclib or plus placebo in postmenopausal women with hormone receptor-positive, HER2-negative locoregionally recurrent or metastatic breast cancer.

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Protocol I3Y-CR-JPBQ  
Phase 3

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 08-Mar-2019  
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bellow:

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## 2. Table of Contents

Section	Page
1. Statistical Analysis Plan: I3Y-CR-JPBQ: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Compare NSAI (Anastrozole or Letrozole) plus Abemaciclib, a CDK4 and CDK6 Inhibitor, or plus Placebo, and to Compare Fulvestrant plus Abemaciclib or plus Placebo in Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer .....	1
2. Table of Contents.....	2
3. Revision History .....	6
4. Study Objectives .....	7
4.1. Primary Objective .....	7
4.2. Secondary Objectives .....	7
4.3. Exploratory Objectives.....	7
5. Study Design.....	8
5.1. Summary of Study Design.....	8
5.2. Determination of Sample Size .....	9
5.3. Method of Assignment to Treatment .....	10
6. A Priori Statistical Methods .....	12
6.1. General Considerations .....	12
6.1.1. Populations .....	12
6.1.2. Definitions and Conventions .....	12
6.2. Handling of Dropouts or Missing Data.....	13
6.3. Patient Disposition .....	13
6.4. Patient Characteristics .....	14
6.4.1. Demographics and Performance Status.....	14
6.4.2. Baseline Disease Characteristics .....	14
6.4.3. Historical Illnesses .....	15
6.4.4. Prior Therapies.....	15
6.4.5. Post Study Treatment Discontinuation Therapies .....	15
6.5. Treatment Compliance .....	16
6.6. Concomitant Therapy.....	16
6.7. Efficacy Analyses .....	16
6.7.1. Primary Endpoint: Progression Free Survival of Cohort A .....	16
6.7.1.1. Definition .....	16
6.7.1.2. Hypotheses and Analysis .....	17

6.7.1.3.	Additional Analyses of the Primary Outcome .....	18
6.7.1.3.1.	Progression-Free Survival Curves and Hazard Ratio .....	18
6.7.1.3.2.	Restricted Mean Difference .....	18
6.7.2.	Secondary Efficacy Analyses .....	19
6.7.2.1.	Progression Free Survival of Cohort B.....	19
6.7.2.2.	Overall Survival .....	19
6.7.2.3.	Objective Response Rate, Disease control Rate, and Clinical Benefit Rate .....	20
6.7.2.4.	Duration of Response .....	20
6.7.3.	Sensitivity Analyses .....	21
6.8.	Health Outcomes/Quality-of-Life Analyses .....	21
6.8.1.	Instruments .....	21
6.8.2.	Quality of Life .....	21
6.8.3.	Pain Intensity and Pain Assessment.....	21
6.9.	Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods.....	22
6.10.	Safety Analyses.....	22
6.10.1.	Extent of Exposure.....	22
6.10.2.	Adverse Events .....	22
6.10.3.	Deaths.....	24
6.10.4.	Clinical Laboratory Evaluation.....	24
6.10.5.	Vital Signs and Other Physical Findings.....	24
6.10.6.	Electrocardiograms .....	24
6.11.	Subgroup Analyses.....	24
6.12.	Protocol Violations.....	25
6.13.	Interim Analyses and Data Monitoring.....	25
6.14.	Annual Report Analyses.....	27
6.15.	Clinical Trial Registry Analyses .....	27
7.	Unblinding Plan .....	28
8.	References .....	29

**Table of Contents**

<b>Table</b>		<b>Page</b>
Table JPBQ.6.1.	Rules for Determining Date of Progression or Censor for Progression-Free Survival .....	17
Table JPBQ.6.2.	Properties of Design for Progression-Free Survival.....	18

Table of Contents

Figure

Page

Figure JPBQ.5.1 Illustration of study design. ....8

### 3. Revision History

SAP Version 1 was approved prior to unblinding.

SAP Version 2 was approved prior to the first unblinded interim efficacy analysis by the DMC. The overall changes incorporated in Version 2 are summarized as follows:

- Updates to the plan of final analysis of Cohort A and Cohort B in different scenarios.
- Updates to details of analysis plan for baseline disease characteristics and subgroup analyses.
- Other minor editorial changes to add clarity.

## 4. Study Objectives

### 4.1. Primary Objective

The primary objective of this study is to compare treatment with abemaciclib plus NSAI (anastrozole or letrozole) therapy versus placebo plus NSAI therapy with respect to PFS in postmenopausal women with HR+, HER2- locoregionally recurrent or metastatic breast cancer.

### 4.2. Secondary Objectives

The key secondary objective of this study is to compare treatment with abemaciclib plus fulvestrant therapy versus placebo plus fulvestrant therapy with respect to PFS for postmenopausal women with HR+, HER2- locoregionally recurrent or metastatic breast cancer. Other secondary objectives of this study are to compare the combination treatment of abemaciclib and NSAI therapy versus placebo plus NSAI therapy, and to compare the combination treatment of abemaciclib and fulvestrant therapy versus placebo plus fulvestrant therapy with respect to the following:

- OS
- OS rate at 1 and 2 years
- objective response rate (complete response [CR] + PR)
- duration of response (DoR; CR + PR)
- disease control rate (DCR; CR + PR + stable disease [SD])
- clinical benefit rate (CBR; CR + PR + SD  $\geq$ 6 months)
- safety and tolerability
- change in symptom burden from baseline using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
- PK of abemaciclib, its metabolites, NSAI, and fulvestrant.

### 4.3. Exploratory Objectives

The exploratory objectives of this study are:

- to compare the combination treatment of abemaciclib and NSAI therapy versus placebo plus NSAI therapy, and to compare the combination treatment of abemaciclib and fulvestrant therapy versus placebo plus fulvestrant therapy with respect to change in pain burden using the modified Brief Pain Inventory short form (mBPI-sf).
- to explore potential biomarkers related to the mechanism of action of abemaciclib, NSAI, fulvestrant, the cell cycle, and/or the pathogenesis of breast cancer, and to correlate potential biomarkers to clinical outcomes.
- to explore if change in tumor size (CTS) is associated with PFS and OS.

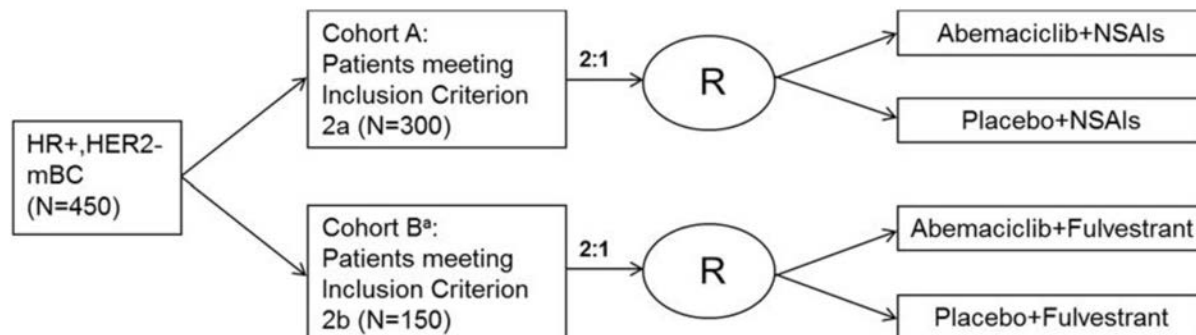


## 5. Study Design

### 5.1. Summary of Study Design

Study JPBQ is a multicenter, randomized, double-blind, Phase 3 trial for women with HR+, HER2- locoregionally recurrent or metastatic breast cancer.

Figure JPBQ.5.1 illustrates the study design.



Abbreviations: HER2- = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; mBC = metastatic breast cancer; N = number of planned patients; NSAI = nonsteroidal aromatase inhibitor; R = randomization

a The initiation of enrollment for patients in Cohort B was triggered later according to Lilly global strategy.

#### Figure JPBQ.5.1 Illustration of study design.

The study will consist of 2 patient cohorts:

- Cohort A will include approximately 300 patients with HR+, HER2- locoregionally recurrent or metastatic breast cancer who meet Inclusion Criterion 2a (Protocol Section 7.1).
- Cohort B will additionally include approximately 150 patients with HR+, HER2- locoregionally recurrent or metastatic breast cancer who meet Inclusion Criterion 2b (Protocol Section 7.1).

Patients in each cohort will be randomized 2:1 between the experimental and control arms:

- Arm A1: Abemaciclib 150 mg orally Q12H on Days 1 to 28 plus either anastrozole 1 mg or letrozole 2.5 mg orally Q24H of a 28-day cycle
- Arm A2: Placebo orally Q12H on Days 1 to 28 plus either anastrozole 1 mg or letrozole 2.5 mg orally Q24H of a 28-day cycle
- Arm B1: Abemaciclib 150 mg orally Q12H on Days 1 to 28 of a 28-day cycle plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond
- Arm B2: Placebo orally Q12H on Days 1 to 28 of a 28-day cycle plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond

Patients in Cohort A will be randomized using the following stratification factors: nature of disease (visceral metastases vs. non-visceral metastases) and prior (neo)adjuvant endocrine therapy (prior therapy with disease-free interval >12 months from completion of treatment vs. prior therapy with disease-free interval ≤12 months from completion of treatment vs. no prior therapy). The presence of visceral metastases refers to lung, liver, pleural, peritoneal, or adrenal gland involvement at the time of randomization.

Patients in Cohort B will be randomized using the following stratification factors: nature of disease (visceral metastases vs. non-visceral metastases) and sensitivity to endocrine therapy (primary resistance vs. secondary resistance). The presence of visceral metastases refers to lung, liver, pleural, or peritoneal, or adrenal gland involvement at the time of randomization. Primary clinical resistance to endocrine therapy is defined as follows: 1) for endocrine therapy in the adjuvant setting, recurrence within the first 2 years of adjuvant endocrine therapy while on endocrine therapy, or 2) for endocrine therapy in the locoregionally recurrent or metastatic setting, progression within first 6 months of initiating first-line endocrine therapy while on endocrine therapy. Patients receiving prior endocrine therapy who do not meet the definition of primary clinical resistance will be considered to have secondary clinical resistance.

The primary analysis of the PFS endpoint will occur after approximately 170 PFS events have been observed in Cohort A. An interim analysis will be conducted after approximately 119 PFS events are observed to provide early efficacy information and allow for potential early communication with regulatory agencies (see Protocol Section 12.2.6 for details).

The interim analysis of Cohort B will follow the timeline of Cohort A, which will occur only if the interim of Cohort A turns out to be positive. If patients in Cohort A continue being followed for PFS until final analysis, the final analysis of Cohort B will be conducted at the same time of Cohort A final analysis. If Cohort A stops early at interim due to efficacy, the final analysis of Cohort B may be conducted after approximately 105 PFS events have been observed in Cohort B. (see Protocol Section 12.2.14 for details).

For each cohort, all patients will be followed for progression and survival information until death or study completion, whichever occurs first.

## 5.2. Determination of Sample Size

The study plan is to enroll approximately 450 patients in total, with 300 HR+, HER2- locoregionally recurrent or metastatic breast cancer patients who have not received prior endocrine therapy in Cohort A and 150 HR+, HER2- locoregionally recurrent or metastatic breast cancer patients in Cohort B. Assuming approximately 10% screening failure, the study will enter approximately 500 patients.

The approximate 300 patients qualified for Cohort A will be randomized in a 2:1 ratio to Arm A1 (abemaciclib plus NSAI; 200 patients) and Arm A2 (placebo plus NSAI; 100 patients). Patients will be randomized using the following stratification factors: nature of disease (visceral metastases vs. non-visceral metastases) and prior (neo)adjuvant endocrine therapy (prior therapy

with disease-free interval > 12 months from completion of treatment vs. prior therapy with disease-free interval ≤ 12 months from completion of treatment vs. no prior therapy).

A 2-look group-sequential design of the primary endpoint will be used to accommodate an event driven plan for the interim and primary PFS analyses (see protocol Section 12.2.6 for details). The primary PFS analysis will be performed after approximately 170 PFS events in Cohort A have occurred (ie, approximately 43% censoring rate). Assuming a hazard ratio of 0.626, this sample size yields at least 81.4% statistical power to detect superiority of the abemaciclib plus NSAI arm over the placebo plus NSAI arm with the use of a 1-sided log-rank test and a type I error of 0.025. If the true median PFS for the placebo plus NSAI arm is 14.4 months, then the hazard ratio of 0.626 amounts to an approximately 8.6-month (59.7%) improvement in median PFS for the abemaciclib plus NSAI arm under an additional assumption of exponential survival distribution.

Approximately 150 patients will be randomized in a 2:1 ratio to Arm B1 (abemaciclib plus fulvestrant; 100 patients) and Arm B2 (placebo plus fulvestrant; 50 patients). Patients will be randomized using the following stratification factors: nature of disease (visceral metastases vs. non-visceral metastases) and sensitivity to endocrine therapy (primary resistance vs. secondary resistance).

The design of Cohort B is to ensure 100 patients' exposure of abemaciclib plus fulvestrant and to show 50% of the global study JPBL trial effect size with roughly 80% probability (ie, 80% of chance to observe a hazard ratio less than 0.824, assuming a true hazard ratio of 0.703 by study assumption).

Here, the effect size of the drug is defined as:

$$\delta = \frac{1}{HR} - 1 = \frac{1 - HR}{HR} = \frac{MST_{Test} - MST_{Control}}{MST_{Control}}$$

$MST_{Test}$  and  $MST_{Control}$  are median survival time in test drug group and control drug group, respectively; effect size can be regarded as the percent change of median survival time.

### 5.3. Method of Assignment to Treatment

Upon obtaining informed consent, site personnel should access the interactive web response system (IWRS) which will assign a patient number. Patients who meet all criteria for enrollment will be randomly assigned to receive either abemaciclib plus NSAI/fulvestrant or placebo plus NSAI/fulvestrant. Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS. Sites will be prompted to enter the specific NSAI at time of randomization for patients in Cohort A.

Randomization will be stratified by the following in Cohort A: nature of disease (visceral metastases vs. non-visceral metastases), and prior (neo)adjuvant endocrine therapy (prior therapy with disease-free interval > 12 months from completion of treatment vs. prior therapy with disease-free interval ≤ 12 months from completion of treatment vs. no prior therapy).

Randomization will be stratified by the following in Cohort B: nature of disease (visceral metastases vs. non-visceral metastases) and sensitivity to endocrine therapy (primary resistance vs. secondary resistance).

The IWRS will be used to assign abemaciclib or placebo and distribute NSAI/fulvestrant supplied by Lilly. Site personnel will confirm that they have located the correct study medication packages by entering a confirmation number found on the packages into the IWRS.

The period between randomization to blinded study drug and the first dose (Cycle 1, Day 1) should not exceed 7 days.

## 6. A Priori Statistical Methods

### 6.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All confidence intervals (CIs) will be given at a 2-sided 95% level, unless otherwise stated.

The assumptions for each statistical method may be evaluated. If there is violation of assumptions, alternative statistical methods may be used.

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

#### 6.1.1. Populations

The **entered** population includes all patients who sign the informed consent document.

The **enrolled** or **intent-to-treat (ITT)** population includes all randomized patients. Patients will be grouped according to randomized treatment.

The **safety** population includes all randomized patients who received at least one dose of blinded study drug or NSAID/fulvestrant. Patients will be grouped according to treatment received in Cycle 1.

The **per-protocol (PP)** population includes all randomized patients without major protocol deviation that have impact to treatment efficacy. Patients will be grouped according to randomized treatment.

Pharmacodynamic and/or biomarker analyses will be based on the subset of patients from the above populations from whom a valid assay result (according to laboratory guideline) has been obtained.

Unless otherwise stated, disposition analyses will be performed on the entered population, all patient characteristic and efficacy analyses will be performed on the ITT population, and all safety and exposure analyses will be performed on the safety population.

All analyses will be performed by treatment arm within each cohort. Unless otherwise noted, all analyses on the ITT population will be performed by assigned treatment arm and all analyses on the safety population will be performed by actual treatment received.

#### 6.1.2. Definitions and Conventions

**Study drug** refers to abemaciclib or placebo.

**Study treatment** refers to study drug plus NSAID/fulvestrant.

The **date of randomization** is the date the patient was randomly assigned to study treatment using the interactive web response system (IWRS).

The **date of first dose** is the date of the first dose of study drug or NSAID/fulvestrant.

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

The **baseline value of an efficacy assessment** is the last value observed prior to the date of randomization. If a patient's first assessment occurs after 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 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.

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 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 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. Handling of Dropouts or Missing Data

With the exception of dates, missing data will not be imputed. The method of imputation for any dates that are imputed is described in the relevant section.

## 6.3. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, treated in the study, reasons for discontinuation from study treatment, and reasons for discontinuation from study. Reason for discontinuation from both study treatment and the study will be summarized by pre-determined categories. If the reason for discontinuation is adverse event (AE), the associated AE term will be reported.

## 6.4. Patient Characteristics

### 6.4.1. Demographics and Performance Status

Patient demographics will be summarized. Patient demographics will include the following:

- race
- age
- country
- height
- weight
- body mass index (BMI)
- baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS).

### 6.4.2. Baseline Disease Characteristics

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

- Initial pathological diagnosis
- Study entry disease status (de novo metastatic disease vs. metastatic recurrent disease vs. locoregionally recurrent disease) for Cohort A
- Prior (neo)adjuvant endocrine therapy (aromatase inhibitor vs. other vs none)
- Prior (neo)adjuvant chemotherapy (yes or no) for Cohort B
- Prior metastatic endocrine therapy (aromatase inhibitor vs. antiestrogen vs. other vs. none) for Cohort B
- Disease-free interval (DFI)
- Treatment-free interval (TFI) for Cohort A
- Sensitivity to endocrine therapy (primary resistance vs. secondary resistance) for Cohort B
- Nature of disease (visceral metastases vs. non-visceral metastases )
- Measurable vs non-measurable disease
- Number of organs involved (1, 2, or 3+)
- Metastatic site
- Estrogen receptor status
- Progesterone receptor status.

Prior (neo)adjuvant endocrine therapy categories will be reported directly from the ‘Prior (neo)adjuvant endocrine therapy’ electronic case report form (eCRF). Prior metastatic endocrine therapy categories will be reported directly from the ‘Prior metastatic endocrine therapy’ eCRF.

Prior (neo)adjuvant chemotherapy will be reported based on data reported on the ‘Systemic Therapy: Prior for this Cancer’ eCRF.

Disease-free interval (DFI) is defined as the period of time between the completion of adjuvant endocrine therapy and disease recurrence for those patients who received adjuvant endocrine therapy. The categories (e.g. relapsed on or within 1 year vs. more than 1 year from completion of adjuvant endocrine therapy) will be reported directly from the ‘Breast Cancer Characteristics

A\_2' eCRF for Cohort A, and 'Breast Cancer Characteristics - B' eCRF for Cohort B, respectively.

Treatment-free interval (TFI) is defined as the period of time between the end date of adjuvant endocrine therapy and the date of informed consent for those patients who received adjuvant endocrine therapy. It will be calculated as the informed consent date – end date of therapy + 1, based on data reported on the 'Disposition: Study Informed Consent' and 'Systemic Therapy: Prior for this Cancer' eCRFs. If only the month and year of a treatment end date is available, the day will be imputed to the 15th. The categories (de novo metastatic vs. <36 months vs. ≥ 36 months vs. recurrent with no adjuvant endocrine) will be derived and reported.

Nature of disease, disease measurability, metastatic site will be reported directly from the 'Nature of Disease' eCRF. The number of organs involved will be derived from the metastatic sites.

### **6.4.3. Historical Illnesses**

Historical illnesses are clinically relevant events in the past that ended before the screening visit. Historical illnesses (using Preferred Term(s) [PTs] from the most current version of the Medical Dictionary for Regulatory Activities [MedDRA]) will be summarized.

### **6.4.4. Prior Therapies**

Prior radiotherapy, surgery, and systemic therapy will be summarized. Prior radiotherapy and surgery will be categorized by reason for regimen. Prior systemic therapies will be categorized by reason for regimen and specific therapy. Frequency of each specific therapy will be tabulated within each reason for therapy.

For cohort B, most recent systemic therapy and the duration of that therapy will be summarized within each of the following subgroups:

- Patients whose most recent systemic therapy was an adjuvant therapy
- Patients whose most recent systemic therapy was for locally advanced or metastatic disease.

This summary will include median duration of treatment (date of end of therapy – date of start of therapy + 1), median time to progression (date of progression – date of first dose + 1), and frequency of each specific therapy. If only the month and year of a treatment date or progression date is available, the day will be imputed to the 15<sup>th</sup>.

### **6.4.5. Post Study Treatment Discontinuation Therapies**

Therapies received following study treatment discontinuation will be summarized by arm. Therapies will be summarized overall and by category: endocrine therapy or targeted/chemotherapy.



## 6.5. Treatment Compliance

Treatment compliance of abemaciclib/placebo will be measured by pill counts and summarized. 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). The total assigned dose for a patient with no adjustments, omissions, or extensions for logistical reasons is  $150 \text{ mg per dose} \times 2 \text{ doses per day} \times 28 \text{ days} = 8400 \text{ mg}$ .

For cohort A, treatment compliance of NSAID will be measured based on pill count data, and will be summarized. Compliance will be calculated as the ratio of the number of doses taken to the total number of assigned doses (minus any dose adjustments and doses omitted/withheld for medical or logistical reasons). The total assigned dose for a patient with no adjustments, omissions, or extensions due to logistical reasons is  $1 \text{ dose per day} \times 28 \text{ days} = 28 \text{ doses}$ .

For cohort B, fulvestrant is administered in the clinic.

## 6.6. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications will be summarized for the ITT population using the preferred name.

## 6.7. Efficacy Analyses

For cohort A, the stratification factors for the analysis of primary and secondary analyses are:

- nature of disease (visceral metastases vs non-visceral metastases)
- prior (neo)adjuvant endocrine therapy (prior therapy with disease-free interval  $>12$  months from completion of treatment vs. prior therapy with disease-free interval  $\leq 12$  months from completion of treatment vs. no prior therapy).

For cohort B, the stratification factors for the analysis of primary and secondary analyses are:

- nature of disease (visceral metastases versus non-visceral metastases)
- sensitivity to endocrine therapy (primary resistance versus secondary resistance).

The stratification factors are captured in the IWRS and on eCRFs. Unless otherwise specified, all stratified analyses will be based on the stratification factors per eCRF. A cross tabulation of the frequency of each level of each stratification factor per IWRS and eCRF will be produced.

### 6.7.1. Primary Endpoint: Progression Free Survival of Cohort A

#### 6.7.1.1. Definition

The primary efficacy measure is progression-free survival of cohort A as defined by RECIST Version 1.1 and determined by the investigator. The PFS time is measured from the date of randomization to the date of objective progression or the date of death due to any cause, whichever is earlier.

If a patient is not known to have progressed or died at the time of analysis, PFS time will be censored at the last known progression-free assessment. The detailed censoring rules are described in the table below (Table JPBQ.6.1).

**Table JPBQ.6.1. Rules for Determining Date of Progression or Censor for Progression-Free Survival**

Rule	Situation	Date of Progression or Censor	Outcome
1	No baseline tumor assessments	Date of Randomization	Censored
2	No post baseline assessments and no death	Date of Randomization	Censored
3	No documented progression and no death (with a post-baseline tumor assessment)	Date of last adequate tumor assessment	Censored
4	Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last adequate tumor assessment	Censored
5	Documented progression	Date of documented progression. If a tumor assessment was done on multiple days, use the earliest date for that visit.	Progressed
6	Death without documented progression	Date of death	Progressed
7	Documented progression or death after missing $\geq 2$ consecutive post-baseline tumor assessments	Date of last adequate tumor assessment before missed assessments or date of randomization, whichever is later	Censored

Note: Progression-free survival and associated outcome is determined by the earliest of the dates above, if more than 1 situation applies.

### 6.7.1.2. Hypotheses and Analysis

Letting  $S_A(t)$  and  $S_P(t)$  denote the progression free survival functions of Abemaciclib + NSAI and placebo + NSAI respectively, the null hypothesis

$$H_0: S_A(t) = S_P(t)$$

will be tested against the one sided alternative hypothesis

$$H_1: S_A(t) > S_P(t).$$

There is 1 planned interim analysis and 1 primary analysis to test these hypotheses. At each analysis, the hypotheses above will be tested using a one sided stratified log rank test, stratified by nature of disease and prior (neo)adjuvant endocrine therapy.

The interim analysis is planned to take place after approximately 119 (70%) investigator assessed PFS events have occurred. The cumulative 1-sided type I error rate of .025 will be maintained using the O'Brien Fleming boundary.

Therefore, if the interim analysis is performed after exactly 119 events have been observed, a 1-sided p-value of less than 0.0082 (corresponding approximately to an observed hazard ratio <0.627 under an exponential model) will need to be observed to declare statistical significance (see Table JPBQ.6.2).

**Table JPBQ.6.2. Properties of Design for Progression-Free Survival**

Information Fraction	Cumulative Events	Cumulative Alpha Spent	Cumulative Beta Spent	Boundary Reject $H_0$ (1-sided p-value)
0.70	119	0.0082	0	<0.0082
1	170	0.0250	0.2	<0.0223

The actual alpha spent will be calculated based on the actual number of events observed at the time of analysis using software that implements the alpha-spending function noted above (for example, ADDPLAN 6.0 or SAS 9.2).

If the interim analysis crosses the boundary of significance at the pre-specified level, the study is considered positive. If statistical significance is not declared at the interim, the final PFS analysis will be conducted with approximately 170 PFS events. All remaining alpha will be spent at the final analysis on Cohort A. Once statistical significance is declared at either interim analysis or the final analysis, the study is considered positive.

### 6.7.1.3. Additional Analyses of the Primary Outcome

#### 6.7.1.3.1. Progression-Free Survival Curves and Hazard Ratio

The Kaplan-Meier (KM) method (Kaplan and Meier 1958) will be used to estimate the PFS curve for each treatment arm. Point estimates and confidence intervals for the first quartile, median, and third quartile for the PFS curve of each arm will be estimated. The PFS rates for each arm will be compared at 4 months intervals up to 24 months using a normal approximation for the difference between the rates.

A Cox proportional hazard model (Cox 1972) stratified by nature of disease and prior (neo)adjuvant endocrine therapy with treatment as a factor will be used to estimate the HR between the two treatment arms and the corresponding CI and Wald p-value (Agresti 2002).

#### 6.7.1.3.2. Restricted Mean Difference

The common method for describing benefit on the time scale is to calculate the difference in median event time between the two treatment arms. An alternative method for describing benefit on the time scale is to estimate the average difference between the KM curves. This corresponds to calculating the difference in the average time to event for the two treatment arms (Irwin 1949; Karrison 1997; Meier et al. 2004). Similar to the HR, this method uses all of the available information across the KM curves, but has the additional advantage of assessing benefit on the time scale.

To estimate an improvement in PFS with abemaciclib, we will follow the method of Irwin (1949) detailed in Karrison (1997) and Meier (2004) for estimating the ‘difference in average PFS’, which we will refer to more formally as the restricted mean difference in PFS.

The area under each KM curve will be calculated using numerical integration (trapezium rule) per Karrison and implemented in SAS using PROC LIFETEST. The difference between treatment arms and a CI for the difference will be formed.

Since the KM curve may be ill-determined beyond a certain range, or even undefined (if the longest observation is censored), for evaluation and comparison of means, the area under each KM curve will be calculated between time 0 and restriction time  $T$ , which is why this is referred to as a "restricted mean". Following the suggestion of Karrison, the restriction time  $T$  will be chosen as largest time point  $t$  such that the standard error ( $SE$ ) of the survival estimate at time  $t$  in each treatment group is no more than 0.075. For this purpose, we will use the simple, albeit conservative, formula proposed by Peto et al. (1977) for calculating the  $SE$  of  $S(t)$  as  $SE(S(t))=S(t) \cdot \frac{1 - S(t)}{n(t)}$ , where  $n(t)$  is the number of patients still at risk at time  $t$ .

## 6.7.2. Secondary Efficacy Analyses

### 6.7.2.1. Progression Free Survival of Cohort B

Progression-free survival in Cohort B is the key secondary endpoint for this study. The measurement, rules of censoring of PFS in cohort B are the same as those of PFS in Cohort A (refer to section 6.7.1). Only if statistical significance is declared at the Cohort A interim analysis, the interim analysis of Cohort B will be conducted based on the same data cutoff. If patients in Cohort A continue being followed for PFS until final analysis, the final analysis of Cohort B will be conducted at the same time of Cohort A final analysis. If Cohort A stops early at interim due to efficacy, the final analysis of Cohort B may be conducted after approximately 105 PFS events have been observed in Cohort B (that is, an approximately 30% censoring rate).

Similar to the analysis of PFS of cohort A, the KM method will be used to estimate the PFS curve for each treatment arm. A Cox proportional hazard model stratified by nature of disease and prior (neo)adjuvant endocrine therapy with treatment as a factor will be used to estimate the HR between the two treatment arms and the corresponding CI.

There will be no alpha spent for any test on this endpoint. Statistical tests, such as stratified log rank test and Wald test, will be purely descriptive.

### 6.7.2.2. Overall Survival

**Overall Survival (OS):** OS duration is measured from the date of randomization of any study drug to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cutoff date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data inclusion cutoff date (contacts considered in the determination of last contact date include AE date, lesion assessment date, visit date, and last known alive date).

The final analysis of OS will be conducted together with the analysis of PFS at study completion. Overall survival, 1-year survival rate and 2-year survival rate by treatment will be analyzed for each cohort.

Kaplan-Meier method and the stratified Cox proportional hazard model will be applied.

### **6.7.2.3. Objective Response Rate, Disease control Rate, and Clinical Benefit Rate**

Objective response rate (ORR), disease control rate (DCR), and clinical benefit rate (CBR) are summary measures of best overall response (BOR) as defined by RECIST v1.1. BOR is derived from time point responses. All time point responses observed while on study treatment and during the short term follow up period (but before the initiation of post discontinuation therapy) will be included in the derivation. The one exception includes patients who receive surgery and/or radiotherapy for locally advanced breast cancer. For these patients, only those time point responses occurring prior to surgery/radiotherapy will be included in the derivation.

Each patient's BOR will be categorized as CR, PR, SD, progressive disease (PD), or not evaluable (NE). For patients with bone-only nonmeasurable disease (see Section 6.4.2), BOR will be limited to CR, SD, PD, and NE. Patients with SD will be further classified as SD  $\geq$  6 months or SD < 6 months. Stable disease  $\geq$  6 months includes all patients with a best response of SD and a PFS time of  $\geq$  6 months. A BOR of CR or PR will not require confirmation.

**Objective Response Rate (ORR):** The objective response rate is the percentage of patients with a BOR of CR or PR.

**Disease Control Rate (DCR):** The DCR is the percentage of patients with a BOR of CR, PR, or SD.

**Clinical Benefit Rate (CBR):** The CBR is the percentage of patients with a BOR of CR or PR, or SD for at least 6 months.

For each cohort, the ORR, DCR, and CBR of each treatment arm will be calculated using the ITT population. All rates will be compared between treatment arms within the cohort based on a normal approximation for the difference between the rates.

### **6.7.2.4. Duration of Response**

**Duration of Response (DoR):** The DoR time is defined only for responders (patients with a CR or PR). It is measured from the date of first evidence of CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier. It is calculated as date of progression or death – date of first response evaluation of CR or PR + 1. The DoR will be censored according to the same rules as PFS, with the addition of the following rule: if a patient begins post discontinuation therapy, DoR will be censored on the day of the last response evaluation prior to the initiation of post discontinuation therapy.

A Kaplan-Meier analysis of DoR will be performed to estimate the DoR curve for each arm within each cohort.

### **6.7.3. Sensitivity Analyses**

In order to evaluate the robustness of the primary and key secondary analysis, PFS analysis will also be conducted based on the PP population.

In addition, the following sensitivity analyses will be performed for PFS based on ITT population:

**Progression-Free Survival Sensitivity Analysis 1** (censoring for receiving subsequent systemic anticancer therapy): if a patient is initiated on another anticancer therapy prior to objective progression, including any postdiscontinuation treatment systemic therapy, radiotherapy, or surgical intervention, PFS will be censored at the date of the last complete objective progression-free disease assessment before initiation of the new therapy.

**Progression-Free Survival Sensitivity Analysis 2** (nonobjective progression as a PFS event): if a patient is discontinued from study treatment due to investigator determined non-objective progression (for example, symptomatic deterioration), then the patient's PFS time will be calculated using the date of non-objective progression as the progression date.

**Progression-Free Survival Sensitivity Analysis 3** (forward-dating progressions at unscheduled assessments): if a patient has objective progression at an unscheduled disease assessment, then the PFS time for that patient will be forward-dated to the next scheduled disease assessment.

## **6.8. Health Outcomes/Quality-of-Life Analyses**

### **6.8.1. Instruments**

Patient-reported outcomes are measured through the following:

- EORTC QLQ-C30: describe target tumor symptom changes
- modified Brief Pain Inventory, Short Form (mBPI-SF): proportion of patients with “worst pain” increase of 2 points or more at any time on-therapy, compared to baseline

### **6.8.2. Quality of Life**

Data from the EORTC QLQ-C30 (Aaronson et al. 1993) instrument will be scored as described by the European Organization for Research and Treatment of Cancer (EORTC) scoring manual (Fayers et al. 2001).

A mixed effects, repeated measures model will be applied to compare treatment arms by cycle with respect to each instrument. The model will include baseline score as a covariate and an unstructured covariance matrix will be utilized. The analysis will include all cycles for which at least 25% of patients in each arm have an assessment.

### **6.8.3. Pain Intensity and Pain Assessment**

Individual pain items on the mBPI-SF (Cleeland 1991) (that is, worst, least, average, and current pain) will be described using descriptive statistics by treatment arm and cycle. A mixed effects, repeated measures model will be applied to compare treatment arms by cycle with respect to

each item. The model will include baseline score as a covariate and an unstructured covariance matrix will be utilized. The analysis will include all cycles for which at least 25% of patients in each arm have an mBPI-SF assessment.

Corresponding analyses will also be conducted for the mean of 7 pain interference with function items. If a patient does not complete Questions 5a through 5g on the BPI-SF, the mean score for the 7 pain interference items will be calculated based on those answered questions when at least 4 out of 7 questions were completed (that is, at least 50% of the questions were answered).

## **6.9. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods**

Pharmacokinetic (PK) analyses will be performed according to a separate PK analysis plan.

## **6.10. Safety Analyses**

### **6.10.1. Extent of Exposure**

For blinded study drug, extent of exposure will be measured by pill counts and summarized by cycle and cumulatively. The summary will include total dosage taken and dose intensity. 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  $\times$  2 doses per day  $\times$  28 days = 8400 mg. The assigned cumulative dose while on study is 2  $\times$  150 mg  $\times$  number of days on treatment.

For co-administered NSAID, extent of exposure will be measured based on pill count and summarized by cycle and cumulatively. The summary will include total doses taken and dose intensity. Dose intensity will be calculated as the ratio of total doses taken to the assigned number of doses. The assigned number of doses for each patient during each cycle is 1 dose per day  $\times$  28 days = 28 doses. The assigned number of doses while on study is 1 dose per day  $\times$  number of days on treatment.

For fulvestrant, extent of exposure will be measured using the fulvestrant administration eCRF and summarized by cycle and cumulatively. The summary will include total dosage administered and dose intensity. Dose intensity will be calculated as the ratio of total dose administered to the assigned cumulative dose. The assigned cumulative dose for each patient during each cycle is 1000 mg for cycle 1 and 500 mg for cycle 2 and beyond. The assigned cumulative dose while on study is 500 mg + 500 mg  $\times$  number of cycles started.

Dose adjustments and omissions, along with the reason for adjustment or omission, will be summarized for blinded study drug, NSAID and fulvestrant.

### **6.10.2. Adverse Events**

Adverse event (AE) terms and severity grades will be assigned by the investigator using Common Terminology Criteria for Adverse Events (CTCAE) Version 4. In addition, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within MedDRA. Adverse events will be reported using the following reporting process:

- The CTCAE Version 4 term reported by the investigator will be mapped to the MedDRA PT and system organ class (SOC) of the corresponding MedDRA lower level term (LLT), unless the reported CTCAE term is 'Other – specify'.
- If the reported CTCAE term is 'Other – specify' the MedDRA LLT, PT and SOC mapped from the verbatim AE term will be used.
- All listings and summaries will use the PT resulting from this process.

Pre-existing conditions are defined as AEs that begin prior to the first dose of study drug.

A treatment emergent adverse event (TEAE) is defined as any AE that begins on or after the day of first dose or any pre-existing condition that increases in CTCAE grade on or after the day of first dose. Comparisons of pre-existing conditions to on-treatment events at the LLT level will be used in the treatment-emergent computation.

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.

AE will also be classified based on the relationship to the study treatment.

The following TEAE/SAE listings and summaries will be produced:

- Overview of TEAEs
- Summary of TEAEs by PT (all grade and grade  $\geq 3$ )
- Summary of TEAEs by SOC and PT (all grade and grade  $\geq 3$ )
- Summary of TEAEs by PT and maximum grade (1-5)
- List of SAEs
- Summary of SAEs by SOC and PT (all grade and grade  $\geq 3$ ).

The four summaries will be produced for all TEAEs/SAEs and repeated for TEAEs/SAEs related to study treatment.



### **6.10.3. Deaths**

All deaths on study 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.

### **6.10.4. Clinical Laboratory Evaluation**

All relevant hematology and chemistry laboratory values will be graded according to CTCAE Version 4. These calculated grades will be summarized by cycle and maximum post-baseline grade over the entire study.

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

Temperature, blood pressure, pulse rate, respiration rate, weight and ECOG PS will be summarized by cycle.

### **6.10.6. Electrocardiograms**

Local electrocardiograms (ECGs) will be summarized by cycle and overall. The summary by cycle will classify patients as having normal or abnormal ECG and summarize AEs identified by ECG within each cycle. The overall summary will classify patients as having an abnormal ECG at any point and summarize all AEs identified by ECG.

## **6.11. Subgroup Analyses**

Subgroup analyses of PFS will be performed for each of following potential prognostic subgroup variables for Cohort A:

- All baseline stratification factors
- Nonsteroidal aromatase inhibitor received at cycle 1 (letrozole vs. anastrozole)
- Study entry disease status (de novo metastatic vs. recurrent metastatic vs. locoregionally recurrent)
- Measurable disease at baseline (yes vs. no)
- Number of organs involved (1 vs. 2 vs. 3+)
- Age (<65 years vs. ≥65 years)
- Country (China vs. non-China)
- PgR status (positive vs. negative)
- Tumor grade (high vs. low/intermediate vs. unknown)
- Liver metastatic (yes vs. no)
- Treatment-free interval (de novo metastatic vs. <36 months vs. ≥ 36 months vs. recurrent with no adjuvant endocrine)
- Baseline ECOG PS (0 vs.1).

Subgroup analyses of PFS will be performed for each of following potential prognostic subgroup variables for Cohort B:

- All baseline stratification factors
- Measurable disease at baseline (yes vs. no)

- Number of organs involved (1 vs. 2 vs. 3+)
- Age (<65 years vs. ≥65 years)
- Country (China vs. non-China)
- PgR status (positive vs. negative)
- Tumor grade (high vs. low/intermediate vs. unknown)
- Liver metastatic (yes vs. no)
- Baseline ECOG PS (0 vs.1)
- Received prior (neo)adjuvant chemotherapy (yes vs. no)
- Received prior endocrine therapy (tamoxifen only vs. AIs only vs. both)
- Most recent endocrine therapy (AIs vs. other ET)
- Most recent endocrine therapy ((neo)adjuvant vs. locally advanced/metastatic)
- Received prior AI (yes vs. no)
- Prior lines of ET (1 line vs 2 lines vs 2+)

If a level of a factor consists of fewer than 10% of randomized patients, analysis within that level will be omitted.

Analyses will be done within subgroup and, separately, across subgroups with a test of interactions of subgroups with treatment performed. Estimated HRs and CIs for the within subgroup analyses will be presented as a forest plot along with p-values for tests of interactions between subgroup variables and treatment.

Other subgroup analyses may be performed as deemed appropriate. If any safety analyses identify important imbalances between arms, subgroup analyses of these endpoints may be performed.

## 6.12. Protocol Violations

Important protocol deviations (IPD) or protocol violations that could potentially impact data interpretation, data integrity and patient safety across the study will be identified from the clinical database and from site monitoring. Categories of IPDs will be documented in the trial issue management plan that will contain detailed criteria used to identify IPDs.

After further review, a comprehensive listing of patients with major protocol deviations among IPDs that might have significantly affected the data interpretation and integrity or patient safety will be provided. A summary of all IPDs by treatment group and overall, as well as a listing of all IPDs will also be provided.

## 6.13. Interim Analyses and Data Monitoring

An interim analysis will be conducted under the auspices of a DMC according to the specifications set forth in the protocol.

An interim analysis on Cohort A will be conducted by the DMC after approximately 119 PFS events have been observed. The interim analysis will be conducted to provide early efficacy information and could potentially result in early communication with regulatory agencies. The O'Brien Fleming alpha spending function (Lan and DeMets 1983) will be used to preserve the

overall type I error. If the analysis of PFS is significant using the p-value boundary described in Section 6.7.1.2, the DMC will be instructed to engage the SMD, who may subsequently convene an IRC to propose actions based upon the DMC's recommendation. All patients will continue follow-up for PFS until study completion, and will remain blinded for the duration of the study unless emergency unblinding (Protocol Section 9.5.2) are met. If Cohort A show early efficacy at interim, the sponsor may consider early stop, unblinding and crossover for this cohort; however, regulatory agencies will be consulted before any action is taken.

The unblinded analysis, including review of the efficacy along with the safety data, will be conducted by the DMC. Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

At the time of the interim analysis, analyses of PFS provided to the DMC will include:

- the boundary values for significance based on the exact number of observed events,
- the p-value for a stratified log rank test comparing the two treatment arms, stratified by the randomization factors,
- an estimate of the HR between the two arms based on a Cox proportional hazards model, stratified by the randomization factors, and
- a KM analysis by treatment arm.

Safety evaluation will be based, at least, on the following data reports:

- summary of patient discontinuations and reasons for discontinuation
- summary of SAEs
- Lilly Safety System reports for all patients with SAEs
- summary of TEAEs

Details pertaining to the conduct of these analyses are provided in the JPBQ DMC Charter.

If statistical significance is not declared at the interim, a final analysis of Cohort A will be conducted with about 170 PFS events.

The interim analysis of Cohort B is triggered only if statistical significance is declared at the Cohort A interim analysis. No DMC is required for the analysis of Cohort B. The analysis will provide both safety and efficacy information of Cohort B and could potentially result in early communication with regulatory agencies, including consultation of potential decisions regarding early stop, unblinding and crossover before any action is taken.

In the case of early stop and crossover for Cohort A or Cohort B after the interim analysis, Lilly will notify investigators when the crossover begins.

If patients in Cohort A continue being followed for PFS until final analysis, the final analysis of Cohort B will be conducted at the same time of Cohort A final analysis. If Cohort A stops early at interim due to efficacy, the final analysis of Cohort B may be conducted after approximately 105 PFS events have been observed in Cohort B.

## 6.14. Annual Report Analyses

Annual report analyses, including Developmental Safety Update Report (DSUR) and Investigational Brochure (IB) analyses, are described in the abemaciclib Program Safety Analysis Plan.

## 6.15. 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](http://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.

In addition, a participant flow will be created that will describe how many enrolled patients completed the study, and for those who did not, the frequency of each reason for not completing. This analysis will be based on study discontinuation, not treatment discontinuation. A patient will be identified as having completed the study if the patient dies while on the study or the patient had discontinued study treatment and is in follow up at the time of the final analysis. Patients who withdraw consent before the final analysis or who are still on treatment at the time of the final analysis will be identified as not completing the study.

## 7. Unblinding Plan

Randomization will occur using an IWRS system. Assignment to treatment groups within a cohort will be determined by a computer-generated random sequence. Security measures will be taken so that treatment group code that can link patients to study arm will be blinded in the database.

In order to maintain the scientific integrity of this double-blind trial, access to study data will be strictly controlled prior to the interim and final analyses. Dummy treatment assignment will be used in the reporting database until the database lock for the final analysis. During this time, analyses using unblinded treatment codes will be performed only at the interim analysis points specified in the protocol/SAP. For those safety and efficacy analyses assigned to the DMC, only the designed Statistical Analysis Center (SAC), who is independent of the sponsor, will perform analyses on unblinded data.

Data sets will be created for the purpose of aggregate data review by the sponsor in which treatment assignment is scrambled so that personnel involved in the day-to-day conduct of the trial and development and validation of analysis programs will be blinded to patient treatment assignment.

While every effort will be made to blind both the patient and the investigator to the identity of the treatment, the inadvertent unblinding of a patient may occur. This unblinding will not be sufficient cause (in and of itself) for that patient to be excluded from any safety or efficacy analyses.

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