Protocol I3Y-MC-JPBL (a)

MONARCH 2: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer

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Approval Date: 12-Jan-2015

1. Protocol I3Y-MC-JPBL

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LY2835219 (Abemaciclib)

This study is a global, multicenter, double-blind, placebo-controlled, Phase 3 trial for women with hormone receptor positive, HER2 negative locally advanced or metastatic breast cancer randomized to receive fulvestrant with or without abemaciclib.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Approved by Lilly: 01 April 2014
Amendment (a) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 12-Jan-2015 GMT

2. Synopsis

Study Rationale

Abemaciclib is an oral, selective, and potent small molecule cyclin-dependent kinases (CDKs) 4 and 6 (CDK4/6) dual inhibitor with antitumor activity within multiple preclinical pharmacology models and an acceptable toxicity profile in nonclinical species. Abemaciclib mesylate has been shown to significantly inhibit tumor growth in multiple murine xenograft models for human cancer. Published studies that evaluated in vitro growth inhibition with other CDK4/6 inhibitors across a diverse panel of 47 breast cell lines showed greater sensitivity to CDK4/6 inhibition in estrogen receptor positive (ER+) lines. Specifically, studies with abemaciclib indicate differential sensitivity to CDK4/6 inhibition based on histological and genetic characteristics. Growth inhibition in vitro across a diverse panel of 46 breast cancer cell lines, representing the known molecular subgroups of breast cancer, indicates that sensitivity to CDK4/6 inhibition is greater in ER+ breast cancers with luminal histology.

Importantly, abemaciclib has demonstrated evidence of clinical activity in a tumor-specific cohort of women with metastatic breast cancer (mBC). In Study I3Y-MC-JPBA, 47 patients with a median of 7 prior systemic regimens received therapy with abemaciclib. Among the 36 patients with hormone receptor positive (HR+) mBC, the median progression-free survival (PFS) was 8.8 months and there were 12 confirmed partial responses (PR) for an objective response rate of 33.3%. In the same study, the combination of abemaciclib plus fulvestrant was also evaluated and demonstrated an acceptable safety profile in 19 women with HR+ mBC. In addition, 4 confirmed partial responses were observed in these 19 patients. These results support further investigation of abemaciclib in combination with fulvestrant for women with HR+ locally advanced or metastatic breast cancer.

Study I3Y-MC-JPBL is a randomized, double-blind, placebo-controlled Phase 3 study of fulvestrant with or without abemaciclib for women with HR+, human epidermal growth factor receptor 2 negative (HER2-) locally advanced (not amenable to curative treatment by surgery) or metastatic breast cancer.

Clinical Protocol Synopsis: Study I3Y-MC-JPBL

Name of Investigational Product: Abemaciclib (LY2835219)	
Title of Study: MONARCH 2: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer	
Number of Planned Patients: 550 Entered: 600 Enrolled: 550 Completed: 550	**Phase of Development:** 3
Length of Study: Approximately 72 months Planned first patient visit: July 2014 Planned last patient visit: August 2020 Planned interim analysis: 270 progression-free survival (PFS) events	

Objectives: The primary objective of Study I3Y-MC-JPBL (JPBL) is to compare abemaciclib plus fulvestrant versus placebo plus fulvestrant with respect to PFS for women with HR+, HER2- locally advanced or metastatic breast cancer.

The secondary objectives of the study are to compare abemaciclib plus fulvestrant versus placebo plus fulvestrant with respect to each of the following:

- overall survival (OS)
- OS rate at 1, 2, and 3 years
- objective response rate [complete response (CR) + partial response (PR)]
- duration of response (DoR) [CR + PR]
- disease control rate (DCR) [CR + PR + stable disease (SD)]
- clinical benefit rate (CBR) [CR + PR + SD ≥6 months]
- safety and tolerability using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 4.0)
- pain and symptom burden using the Brief Pain Inventory (BPI), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the EORTC QLQ-BR23 (breast) questionnaires, and health status scores from the EuroQol 5-Dimension 5 Level (EQ-5D 5L)
- pharmacokinetics (PK) of abemaciclib, its metabolites, and fulvestrant
- time to worsening of Eastern Cooperative Oncology Group (ECOG) performance status of ≥2
- time to first skeletal-related event (SRE; defined as either pathological fracture, spinal cord compression, radiation to the bone, or surgery to the bone)

The exploratory objectives are:

- To explore potential biomarkers related to the retinoblastoma (Rb) pathway and/or the pathogenesis of breast cancer
- To explore if change in tumor size is associated with PFS and OS
- To explore time to progressive bone metastases by treatment arm

Study Design: Study JPBL is a multicenter, randomized, double-blind, Phase 3 trial for women with HR+, HER2- locally advanced or metastatic breast cancer. Approximately 550 patients will be randomized 2:1 between the 2 arms. Patients will be randomized using the following stratification factors: nature of disease (visceral metastases versus bone only metastases versus other) and sensitivity to endocrine therapy (no prior endocrine therapy versus primary resistance versus secondary resistance). The presence of visceral metastases refers to lung, liver, pleural, or peritoneal 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 locally advanced 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.

Diagnosis and Main Criteria for Inclusion and Exclusions: Patients are eligible to be included in the study if they meet following criteria: 1) have a diagnosis of HR+, HER2- breast cancer; 2) have inoperable locally advanced or metastatic disease and relapsed with radiologic evidence of progression after prior endocrine therapy or have not received prior endocrine therapy; 3) have postmenopausal status due to either surgical/natural menopause or ovarian suppression with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin; 4) have a negative serum pregnancy test at baseline (within 14 days prior to randomization) and agree to use medically approved precautions to prevent pregnancy during the study and for 12 weeks following the last dose of abemaciclib if postmenopausal status is due to ovarian suppression with a GnRH agonist; 5) have either measurable disease or nonmeasurable bone only disease; 6) are female and $\geq$18 years of age; 7) have given written informed consent prior to any study-specific procedures; 8) have adequate organ function; 9) have a performance status $\leq$1 on the ECOG scale; 10) have discontinued previous therapies for cancer, for at least 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents prior to receiving study drug, and recovered from the acute effects of therapy;11) are willing to participate for the duration of the study and to follow study procedures; and 12) are able to swallow capsules.

Patients will be excluded from the study if they meet any of the following criteria: 13) are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study; 14) have visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis; 15) have a history of central nervous system metastasis; 16) have received prior treatment with chemotherapy (except for neoadjuvant/ adjuvant chemotherapy), fulvestrant, everolimus, or any CDK4/6 inhibitor; 17) have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days prior to randomization of study drug for a nonmyelosuppressive or myelosuppressive agent, respectively; 18) have received recent (within 28 days prior to randomization) yellow fever vaccination; 19) have had major surgery within 14 days prior to randomization; 20) have a personal history of any of the following conditions: presyncope or syncope of either unexplained or cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest; 21) have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study; 22) have inflammatory breast cancer or a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years; 23) have received an autologous or allogeneic stem-cell transplant; 24) have active bacterial or fungal infection, or detectable viral infection; or 25) are pregnant or breastfeeding.

Test Product, Dosage, and Mode of Administration:
Abemaciclib will be supplied as capsules administered orally, 150 mg every 12 hours (Q12H) on Days 1 to 28 of a 28-day cycle, plus fulvestrant will be administered 500 mg intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock, on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond.

Planned Duration of Treatment:
Treatment period: until disease progression or other discontinuation criteria are fulfilled.
Short-term follow-up (postdiscontinuation): 30 days
Long-term follow-up (postdiscontinuation): until death

Reference Therapy, Dose, and Mode of Administration: Placebo will be supplied as capsules administered orally Q12H on Days 1 to 28 of a 28-day cycle plus fulvestrant will be administered 500 mg intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock, on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond.

Criteria for Evaluation:

Efficacy:

- PFS
- OS
- OS at 1, 2, and 3 years
- Objective Response Rate
- DoR
- DCR
- Time to Worsening ECOG Performance Status
- Time to First Skeletal-Related Event (TTFSRE)

Safety:

- Adverse events using NCI CTCAE Version 4.0

Health Outcomes:

- BPI: proportion of patients with "worst pain" increase of 2 points or more at any time on-therapy, compared to baseline
- EORTC QLQ-C30 and EORTC QLQ-BR23: Describe target tumor symptom changes
- EQ-5D 5L: Describe health status changes

Pharmacokinetics:

- Population PK parameters for abemaciclib and fulvestrant
- Plasma concentration levels of fulvestrant during Cycle 1/Cycle 2

Exploratory

- Potential biomarkers related to the Rb pathway and/or the pathogenesis of breast cancer.
- Time course of change in tumor size

Statistical Methods:

Statistical: The primary objective of this study is to compare abemaciclib plus fulvestrant versus placebo plus fulvestrant in terms of PFS for women with HR+, HER2- locally advanced or metastatic breast cancer. An important secondary objective of this study is to compare the 2 arms with respect to OS.

A 2-look group sequential design on the primary endpoint of PFS will be utilized, with interim and primary PFS analyses occurring at approximately 270 PFS events and 385 PFS events, respectively. The Lan-Demets method with an O'Brien-Fleming like spending function will be used to maintain the cumulative 1-sided Type I error rate of .025. Assuming a hazard ratio (HR) of 0.703, this design yields at 90% statistical power to detect superiority of the abemaciclib plus fulvestrant arm over placebo plus fulvestrant arm with the use of a 1-sided log-rank test and a cumulative type I error rate of 0.025.

OS is an important secondary endpoint for this study. OS will be tested only if the test of PFS is significant. A 4-look approach to testing OS with a cumulative 1-sided type I error rate of .025 will be utilized to allow for analyses of OS at the interim PFS analysis, the primary PFS analysis, 289 OS events, and 385 OS events (final OS analysis).

Efficacy:

The PFS and OS analyses to test the superiority of abemaciclib to placebo in improving PFS and OS time will use the log-rank test stratified by stratification variables. Additional analyses will be performed using the Kaplan-Meier method to estimate the PFS and OS curves and rates, and the Cox proportional hazard model will be used to estimate the PFS and OS HRs and corresponding 95% confidence interval.

Safety:

All safety summaries and analyses will be based on the Safety Population, defined as all enrolled patients receiving at least 1 dose of any study drug. Patients will be grouped according to treatment received in Cycle 1.

Health Outcomes:

The maximum change from baseline score will be calculated and summarized for BPI "worst pain" and EORTC composite scores. The number and reason for missing and incomplete questionnaires/assessments will be summarized for each instrument and study arm.

Pharmacokinetics:

PK parameters for abemaciclib in plasma (clearance, exposure, volume of distribution, and half-lives) and inter-individual PK variability will be computed using nonlinear mixed effect modeling implemented in NONMEM. If warranted by the data, PK parameters for fulvestrant in plasma and inter-individual variability estimates will also be computed using nonlinear mixed effect modeling implemented in NONMEM.

Pharmacodynamics:

Pharmacodynamic data (such as neutrophil, lymphocytes, or platelets counts in blood) may be analyzed by means of NONMEM and connected to the population PK model for abemaciclib and/or fulvestrant in a PK/pharmacodynamic model.

Tailoring biomarkers:

Summary statistics will include means, medians, corresponding standard errors, quartiles, and ranges. Biomarkers with discrete measures, such as genotype locus, will be summarized in frequency tables. Correlative analyses may be performed to investigate associations between biomarkers and clinical endpoints.

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
AE	adverse event Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some institutional review boards [IRBs]).
AST	aspartate aminotransferase
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
blinding/masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BPI-sf	Brief Pain Inventory-short form
collection database	A computer database where clinical trial data are entered and validated.
CRF/eCRF	case report form/electronic case report form Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CI	confidence interval

complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC BR23	EORTC Breast subscale, 23 items
ERB/IRB	ethical review board/institutional review board A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
EQ-5D 5L	EuroQol 5-Dimension 5 Level
extension period	The period between study completion and end of trial during which patients on study therapy who continue to experience clinical benefit may continue to receive study therapy until one of the criteria for discontinuation is met.
FSH	follicle-stimulating hormone
GCP	good clinical practice
GnRH	gonadotropin-releasing hormone

HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug application
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
ITT	intention-to-treat The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web response system
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LLT	Lower Level Term
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute

OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PR	partial response
PRO/ePRO	patient-reported outcome/electronic patient-reported outcome
PS	performance status
PT	Preferred Term
randomize	the process of assigning patients to an experimental group on a random basis
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
SAP	Statistical Analysis Plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SMD	Lilly Senior Management Designee
SOC	System Organ Class
SRE	skeletal-related event
Study completion	This study will be considered complete following evaluation of additional overall survival data as determined by Lilly.

SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
ULN	upper limits of normal
US	United States
VAS	visual analog scale

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5. Introduction

Breast cancer is one of the most common cancers among women in the United States and Europe and is the second leading cause of cancer death in women. Early stage disease is treatable, but metastatic breast cancer (mBC) has a median overall survival (OS) of only 2 to 3 years (Cardoso et al. 2012). While women who have been diagnosed with hormone receptor positive (HR+) mBC are typically treated with endocrine therapy, de novo or acquired resistance to endocrine therapy is a common clinical problem in this population. Clinical studies have demonstrated that cyclinD is overexpressed in more than 50% of breast cancers, the majority of which are also estrogen receptor positive (ER+). CyclinD interacts directly with cyclin-dependent kinases 4 and 6 (CDK4/6) in an active protein complex. Therefore, CDK4/6 represents a potentially important target to address the unmet need for patients with mBC, in particular those with HR+ disease.

Abemaciclib is a potent and selective small molecule inhibitor of CDK4/6. In the Phase 1 Study I3Y-MC-JPBA (JPBA), abemaciclib has shown acceptable safety across five tumor-specific cohorts, with the most common treatment-emergent adverse events (TEAEs) possibly related to study drug including diarrhea, nausea, fatigue, vomiting, and neutropenia. Importantly, abemaciclib has demonstrated evidence of clinical activity in a tumor-specific cohort of women mBC. In Study I3Y-MC-JPBA, 47 patients with a median of 7 prior systemic regimens received therapy with abemaciclib. Among the 36 patients with HR+ mBC, the median progression-free survival (PFS) was 8.8 months and there were 12 confirmed partial responses (PR) for an objective response rate of 33.3%. In the same study, the combination of abemaciclib plus fulvestrant was also evaluated and demonstrated an acceptable safety profile in 19 women with HR+ mBC. In addition, 4 confirmed partial responses were observed in these 19 patients. These results support further investigation of abemaciclib in combination with fulvestrant for women with HR+ locally advanced or metastatic breast cancer.

Study I3Y-MC-JPBL is a randomized, double-blind, placebo-controlled Phase 3 study of fulvestrant with or without abemaciclib for women with HR+, human epidermal growth factor receptor 2 negative (HER2-) locally advanced (not amenable to curative treatment by surgery) or metastatic breast cancer.

More information about the known and expected benefits and risks of abemaciclib may be found in the Investigator's Brochure (IB). Information on adverse events (AEs) expected to be related to the study drug may be found in Section 7 (Development Core Safety Information) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

More detailed information about the known and expected benefits and risks of fulvestrant may be found in the following: Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

5.1. Rationale for Amendment (a)

This protocol was amended so that the initial dose of abemaciclib when administered in combination with fulvestrant could be lowered from 200 mg every 12 hours (Q12H) to 150 mg Q12H.

Additionally, existing patients who have already started on 200 mg of blinded study drug will be dose reduced to 150 mg Q12H.

Further modifications were performed for clarity: 1) blinded study drug in relevant places defined; 2) supportive management for diarrhea modified. Minor typographical and formatting edits were made throughout the document for clarity and consistency.

5.2. Dose Rationale

The rationale for reducing and selecting the starting dose was based on the preliminary blinded safety review of Study JPBL and updated safety and pharmacokinetic/pharmacodynamic (PK/PD) data from patients treated with endocrine therapies in combination with abemaciclib in advanced or metastatic breast cancer enrolled in Studies JPBA and JPBH.

Pharmacokinetic data obtained in Study JPBA for abemaciclib from a total of 124 patients dosed repeatedly with abemaciclib at 150 and 200 mg Q12H indicate that the range of steady-state exposures achieved with 150 mg Q12H is comparable to 200 mg Q12H. In addition, in Study JPBA the steady-state exposures achieved with a 50-mg unit dose, which is the lowest possible allowed dose in Study JPBL in the case of dose reduction when needed for AEs, are within the low end of the range of exposures achieved by the 150- and 200-mg dose levels. Skin biopsies collected in Study JPBA predose and 4 hours postdose on Cycle 1 Day 15 show a decrease in the pRb and topoIIα expression with increasing plasma concentration. Abemaciclib effectively inhibits CDK4/6, which results in cell cycle inhibition upstream of the G1 restriction point at both doses of 150 and 200 mg.

Tumor responses were observed in patients receiving both 150 mg and 200 mg abemaciclib monotherapy. As of 29 August 2014, findings in the 47 patients with advanced or metastatic breast cancer who have been enrolled in Part D of Study JPBA resulted in 12 confirmed PRs (including 8 responses at 150 mg Q12H and 4 responses at 200 mg Q12H) among the 36 patients in Part D with HR+ mBC, based on investigators' assessment of response using RECIST v1.1. The ORR for the 36 patients in Part D with HR+ mBC was 33.3%, the DCR was 80.6%, the CBR was 61.1%, and median PFS was 8.8 months.

In a subsequent cohort of 19 patients with HR+, advanced or metastatic breast cancer enrolled in Part G of Study JPBA and treated with fulvestrant plus 200mg abemaciclib Q12H, 17 patients with abemaciclib dose reductions were observed. In addition, 4 confirmed PRs were observed

for an ORR was 21.1% (36.4% in the 11 patients with measureable disease), the DCR was 78.9%, the CBR was 63.2%, and the median PFS was 10.0 months.

Preliminary safety data from Study JPBH demonstrate that the AE profile of abemaciclib administered in combination with nonsteroidal aromatase inhibitors (NSAIs) is consistent with abemaciclib monotherapy, as the most common TEAEs possibly related to study drug were diarrhea, nausea, fatigue, and neutrophil count decreased. However, at the 200-mg dose, the incidence of treatment-emergent Grade 3 diarrhea was found to be greater when abemaciclib was administered in combination with an NSAI from a review of the preliminary safety data in Study JPBH, compared to abemaciclib administered alone in Part D of Study JPBA. Nevertheless, when the abemaciclib dose was reduced from 200 mg to 150 mg or lower for some patients in Study JPBH, either the severity of diarrhea decreased or the event resolved.

The rationale for the underlying change in the abemaciclib starting dose is, that although the Phase 1 Study JPBA demonstrated that the 200mg Q12H abemaciclib dose was tolerable when administered in combination with fulvestrant, a substantial number of patients required abemaciclib dose suspension and/or reduction during the first 2 treatment cycles. As a consequence of this observation, a review of dosing and tolerability data from patients enrolled during the first 3 months of this study was carried out as part of a regular blinded safety review to assess if a similar number of patients required dose alterations in the present study. During the review of blinded safety data from Study JPBL, any alteration in dosing of abemaciclib or placebo was presumed to have occurred on the abemaciclib arm. The data review did reveal a high number of dose alterations for abemaciclib or placebo. The cause of this was principally diarrhea occurring in the first treatment cycle. Therefore the initial dose of blinded study drug administered in combination with fulvestrant will be reduced to 150 mg Q12H.

6. Objectives

6.1. Primary Objective

The primary objective of Study JPBL is to compare abemaciclib plus fulvestrant versus placebo plus fulvestrant with respect to PFS for women with HR+, HER2- locally advanced or metastatic breast cancer.

6.2. Secondary Objectives

The secondary objectives of the study are to compare abemaciclib plus fulvestrant versus placebo plus fulvestrant with respect to each of the following:

- overall survival (OS)
- OS rate at 1, 2, and 3 years
- objective response rate [complete response (CR) + partial response (PR)]
- duration of response (DoR) [CR + PR]
- disease control rate (DCR) [CR + PR + stable disease (SD)]
- clinical benefit rate (CBR) [CR + PR + SD ≥6 months]
- safety and tolerability using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 4.0)
- pain and symptom burden using the Brief Pain Inventory (BPI), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the EORTC QLQ-BR23 (breast) questionnaires, and health status scores from the EuroQol 5-Dimension 5 Level (EQ-5D 5L)
- pharmacokinetics (PK) of abemaciclib, its metabolites, and fulvestrant
- time to worsening of Eastern Cooperative Oncology Group (ECOG) performance status
- time to first skeletal-related event (SRE; defined as either pathological fracture, spinal cord compression, radiation to the bone, or surgery to the bone)

6.3. Exploratory Objectives

- To explore potential biomarkers related to the retinoblastoma (Rb) pathway and/or the pathogenesis of breast cancer
- To explore if change in tumor size is associated with PFS and OS
- To explore time to progressive bone metastases by treatment arm

7. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

Study participants should be instructed not to donate blood or blood products during the study or for 9 months following the last dose of fulvestrant or 2 weeks following the last dose of blinded study drug, whichever is longer.

Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) is not permitted.

7.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] have a diagnosis of HR+, HER2- breast cancer

- to fulfill the requirement of HR+ disease, a breast cancer must express, by immunohistochemistry (IHC), at least 1 of the hormone receptors (estrogen receptor [ER] or progesterone receptor [PgR]) as defined in the relevant American Society of Clinical Oncology (ASCO) / College of American Pathologists (CAP) Guidelines (Hammond et al. 2010).
- to fulfill the requirement of HER2- disease, a breast cancer must not demonstrate, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 by either IHC or in-situ hybridization as defined in the relevant ASCO / CAP Guidelines (Wolff et al. 2013). Although not required as a protocol procedure, a patient with a new metastatic lesion should be considered for biopsy whenever possible to reassess HER2 status prior to study entry if clinically indicated.

[2] have either locally advanced disease not amenable to curative treatment by surgery or metastatic disease. In addition, patients must fulfill 1 of the following criteria:

- relapsed with radiologic evidence of progression on neoadjuvant or adjuvant endocrine therapy
- relapsed with radiologic evidence of progression within 1 year from completion of adjuvant endocrine therapy
- relapsed with radiologic evidence of progression more than 1 year from completion of adjuvant endocrine therapy and then subsequently relapsed with radiologic evidence of progression after no more than first-line endocrine therapy (with either an antiestrogen or an aromatase inhibitor) for metastatic disease
- presented de novo with locally advanced or metastatic disease and not received any prior endocrine therapy
- presented de novo with locally advanced or metastatic disease and then relapsed with radiologic evidence of progression after no more than first-line endocrine therapy (with either an antiestrogen or an aromatase inhibitor)

[3] have postmenopausal status due to either surgical/natural menopause or ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin. Postmenopausal status due to surgical/natural menopause requires at least 1 of the following:

- prior bilateral oophorectomy
- age ≥60 years
- age <60 years and amenorrheic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and follicle-stimulating hormone (FSH) and estradiol levels in the postmenopausal range

[4] have a negative serum pregnancy test at baseline (within 14 days prior to randomization) and agree to use medically approved precautions to prevent pregnancy during the study and for 12 weeks following the last dose of abemaciclib if postmenopausal status is due to ovarian suppression with a GnRH agonist

[5] have either measurable disease or nonmeasurable bone only disease. Measurable and nonmeasurable disease are defined according to the Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1 [v1.1], Eisenhauer et al. 2009; refer to Attachment 5). Nonmeasurable bone only disease may include any of the following: blastic bone lesions, lytic bone lesions without a measurable soft tissue component, or mixed lytic-blastic bone lesions without a measurable soft tissue component.

[6] are female and ≥18 years of age

[7] have given written informed consent prior to any study-specific procedures

[8] have adequate organ function, including:

- hematologic: absolute neutrophil count ≥1.5 × 10^9/L, platelets ≥100 × 10^9/L, and hemoglobin ≥8 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator; however, initial study drug treatment must not begin earlier than the day after the erythrocyte transfusion.
- hepatic: bilirubin ≤1.5 times upper limit of normal (ULN) and alanine aminotransferase (ALT) ≤3.0 times ULN
- renal: serum creatinine ≤1.5 times ULN

[9] have a performance status ≤1 on the ECOG scale

[10] have discontinued previous therapies for cancer (including specifically, aromatase inhibitors, anti-estrogens, chemotherapy, radiotherapy, and immunotherapy) for at least 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents prior to receiving study drug, and recovered from the acute effects of therapy (until the toxicity resolves to either baseline or at least Grade 1) except for residual alopecia or peripheral neuropathy

[11] are willing to participate for the duration of the study and to follow study procedures

[12] are able to swallow capsules

7.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[13] are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study. If a patient is currently enrolled in a clinical trial involving non-approved use of a device, then agreement with the investigator and Lilly clinical research physician (CRP) is required to establish eligibility.

[14] have visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis. Visceral crisis is not the mere presence of visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease.

[15] have clinical evidence or history of central nervous system metastasis. Screening is not required for enrollment.

[16] have received prior treatment with chemotherapy (except for neoadjuvant/ adjuvant chemotherapy), fulvestrant, everolimus, or any CDK4/6 inhibitor

[17] have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days prior to randomization of study drug for a nonmyelosuppressive or myelosuppressive agent, respectively

[18] have received recent (within 28 days prior to randomization) yellow fever vaccination

[19] have had major surgery within 14 days prior to randomization of study drug to allow for post-operative healing of the surgical wound and site(s).

[20] have a personal history of any of the following conditions: presyncope or syncope of either unexplained or cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest

[21] have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study (for example, history of major surgical resection involving the stomach or small bowel)

[22] have inflammatory breast cancer or a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years

[23] have received an autologous or allogeneic stem-cell transplant

[24] have active bacterial or fungal infection, or detectable viral infection (for example, human immunodeficiency virus [HIV] or viral hepatitis). Screening is not required for enrollment.

[25] are pregnant or breastfeeding

7.3. Discontinuations

7.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor CRP and the investigator to determine whether the patient may continue in the study, with or without study drug. Inadvertently enrolled patients may be maintained in the study and on study drug when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without study drug if the Lilly CRP does not agree with the investigator's determination that it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without study drug.

In addition, patients will be discontinued from the study drug(s) and/or from the study in the following circumstances:

- Progressive disease as defined by RECIST v1.1. A patient who does not fulfill the criteria for progressive disease according to RECIST v1.1 should not be discontinued prior to discussion and agreement between the investigator and the Lilly CRP, unless another discontinuation criterion is fulfilled.
- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- investigator decision
    - the investigator decides that the patient should be discontinued from the study or study drugs
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drugs occurs prior to introduction of the new agent
- patient decision
    - the patient or the patient's designee (for example, parents or legal guardian) requests to be withdrawn from the study or study drug

- sponsor decision
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)

The reason and date for discontinuation will be collected for all patients. All randomized patients who discontinue regardless of whether or not they received study drug will have procedures performed as shown in the Study Schedule (Attachment 1).

7.3.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

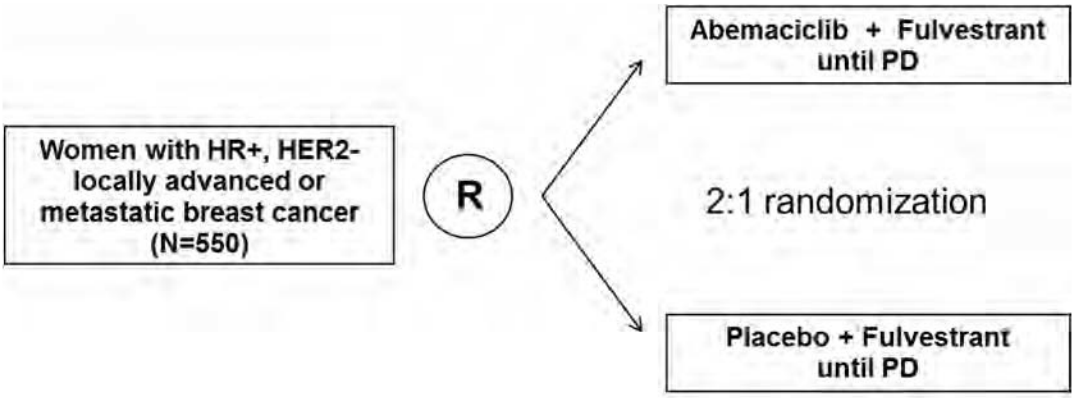
7.3.3. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8. Investigational Plan

8.1. Summary of Study Design

Study I3Y-MC-JPBL (JPBL) is a multicenter, randomized, double-blind, Phase 3 trial for women with HR+, HER2- locally advanced or metastatic breast cancer. Figure JPBL.8.1 illustrates the study design.



Abbreviations: HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2 negative; N = number; PD = progressive disease.

Figure JPBL.8.1. Illustration of study design.

Approximately 550 patients will be randomized 2:1 between the 2 arms:

- Experimental Arm A: 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
- Control (Placebo) Arm B: 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 will be randomized using the following stratification factors: nature of disease (visceral metastases versus bone only metastases versus other) and sensitivity to endocrine therapy (no prior endocrine therapy versus primary resistance versus secondary resistance). The study population will be monitored upon enrollment to include no more than 100 endocrine therapy naïve patients. The presence of visceral metastases refers to lung, liver, pleural, or peritoneal 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 locally advanced 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.

Data base lock for the interim analysis for efficacy will occur when approximately 270 investigator-assessed PFS events have been observed. Database lock for the primary analysis of the PFS endpoint will occur when approximately 385 investigator-assessed PFS events have been observed. All patients will be followed for progression and survival information until death or study completion, whichever occurs first.

Terms used to describe the periods during the study are defined below:

- **Baseline:** begins when the informed consent form (ICF) is signed and ends at the first study treatment (or at discontinuation, if no treatment is given).
- **Study Period:** begins at the first study treatment and ends at study completion. The study period does not include the extension period.
    - **Study Treatment Period:** begins at the first study treatment and ends when the patient and the investigator agree that the patient will no longer continue study treatment. The date of this agreement is to be reported on the electronic case report form (eCRF) as the Date of Discontinuation from study treatment.
    - **Postdiscontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.

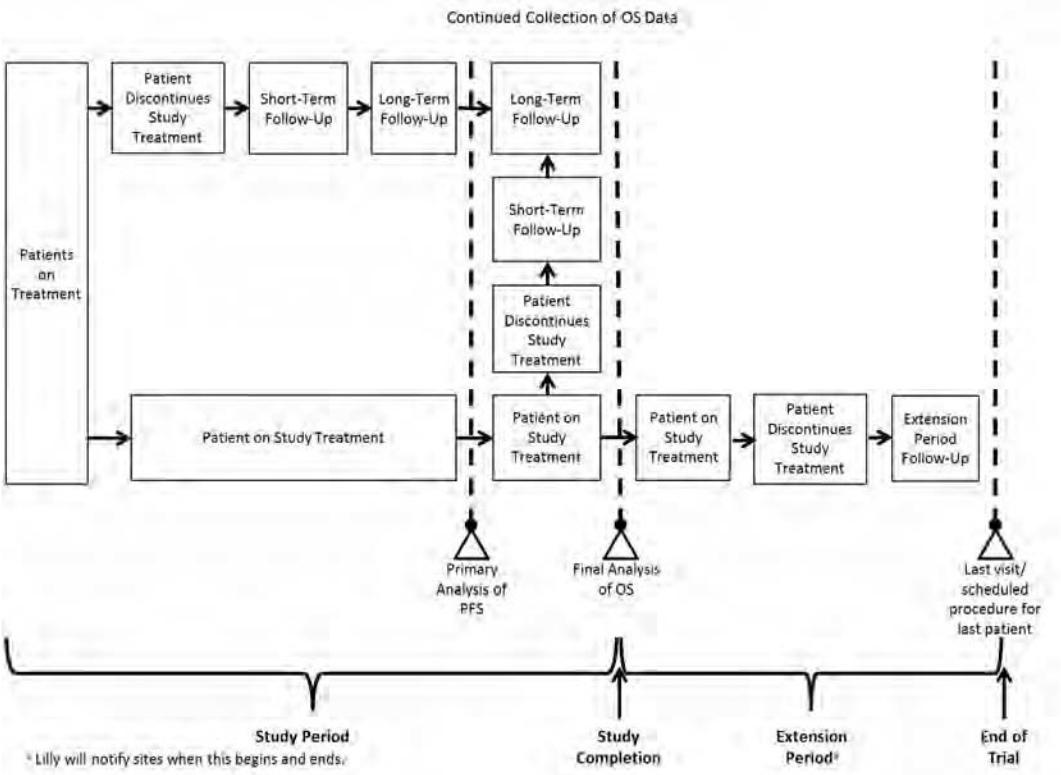
      Short-term follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.

      Long-term follow-up begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion.
- **Extension Period:** begins after study completion and ends at the end of trial. During the extension period, patients on study therapy who continue to experience clinical benefit may continue to receive study therapy until one of the criteria for discontinuation is met. The extension period includes extension period short-term follow-up.
    - Extension period short-term follow-up: begins the day after the patient and the investigator agree that the patient will no longer continue study treatment in the extension period and lasts approximately 30 days.

8.1.1. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the evaluation of final OS data (refer to Figure JPBL.8.2), as determined by Lilly. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed extension period follow-up (Figure JPBL.8.2).



Abbreviations: OS = overall survival; PFS = progression-free survival.

Figure JPBL.8.2. Study period and extension period diagram.

8.1.2. Extension Period

After study completion, all patients who are on study treatment and who are eligible for the extension period will be unblinded. Patients receiving study treatment and experiencing ongoing clinical benefit may continue to receive study treatment in the extension period until one of the criteria for discontinuation is met (Section 7.3). During the extension period, placebo will no longer be administered, and crossover will not be permitted. Lilly will notify investigators when the extension period begins.

Patients who are in short-term follow-up when the extension period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the extension period begins will be discontinued from long-term follow-up.

During the extension period, all AEs, SAEs, and study drug exposure will be reported on the eCRF. Serious adverse events will also be reported to Lilly Global Patient Safety (GPS) (see Section 10.3.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

8.2. Discussion of Design and Control

A randomized, controlled design is being used in this study. Randomization minimizes systematic bias in the selection and assignment of patients to study therapy and provides justification for inferential statistical methods to be used on data from this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study therapy and minimizes bias in the assessment and interpretation of observed treatment effects. Patients will be stratified for differences in factors thought to be associated with clinical outcomes to further reduce the potential for bias and improve the power of the analyses. Assessment of bias is further minimized by the use of a double blind and placebo control. See Section 9.3.

Investigational treatment administration in this study is double-blind; that is, patients, investigational sites, and the sponsor study team do not have immediate access to treatment assignments for any patients. This design feature minimizes potential bias due to knowledge of patient's treatment during evaluation of study endpoints, at the patient level or aggregated across patients.

9. Treatment

9.1. Treatments Administered

The following treatments will be administered in this study:

- Experimental Arm A: 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
- Control (Placebo) Arm B: 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

Blinded study drug is defined as abemaciclib or placebo. Study treatment is defined as blinded study drug and fulvestrant.

For both experimental and control arms, fulvestrant 500 mg should be administered intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock; however, for patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection.

Table JPBL.9.1 shows the treatment regimens.

Table JPBL.9.1. Treatment Regimens/Dosing Schedule

Regimen	Period/Cycle	Dose Day
Experimental Arm A		
Abemaciclib	Treatment/28-day cycle	150 mg PO Q12H on Days 1-28
Fulvestrant	Treatment/28-day cycle	500 mg IM on Days 1 and 15 of Cycle 1, then Day 1 of Cycle 2 and beyond
Control (Placebo) Arm B		
Placebo	Treatment/28-day cycle	PO Q12H on Days 1-28
Fulvestrant	Treatment/28-day cycle	500 mg IM on Days 1 and 15 of Cycle 1, then Day 1 of Cycle 2 and beyond

Abbreviations: IM = intramuscular; PO = orally; Q12H = once every 12 hours.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drugs and planned duration of each individual's treatment to the patient/site personnel/legal representative
- verifying that instructions are followed properly
- maintaining accurate records for dispensing and collection of study drugs
- returning all unused medication to Lilly or its designee at the end of the study

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

9.2. Materials and Supplies

Abemaciclib or placebo (blinded study drug) will be supplied as capsules for oral administration. Blinded study drug capsules should be stored at room temperature according to the product label, and not opened, crushed, or dissolved. Investigators should instruct patients to store the capsules in the original package and in a location inaccessible to children. Blinded study drug will be labeled according to the country's regulatory requirements.

Depending on country requirements, fulvestrant will be supplied by the site or centrally sourced by Lilly as 250-mg prefilled syringes (250 mg/5 mL). Sites should confirm fulvestrant source to ensure adequate supply. Fulvestrant should be stored according to the instructions on the product label and administered according to the instructions in the protocol. Where fulvestrant is supplied by Lilly, it will be labeled according to the country's regulatory requirements.

9.3. 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 fulvestrant or placebo plus fulvestrant. Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS.

Randomization will be stratified by the following: nature of disease (visceral metastases versus bone only metastases versus other) and sensitivity to endocrine therapy (no prior endocrine therapy versus primary resistance versus secondary resistance).

The IWRS will be used to assign abemaciclib/placebo and fulvestrant (where supplied). 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.

9.4. Selection and Timing of Doses

Blinded study drug will be taken orally every 12 (±2) hours on Days 1 through 28 of a 28-day cycle, for a total of 56 doses per cycle. Patients should not consume food beginning 1 hour before and ending 1 hour after taking blinded study drug. During all cycles, blinded study drug should be taken at approximately the same times each day. If a patient misses or vomits a dose, that dose should be omitted.

Fulvestrant should be administered at the same time as (or up to 20 minutes after) the morning dose of blinded study drug, except when specified otherwise in the PK Sampling Schedule (Attachment 7). Fulvestrant will be administered intramuscularly on Days 1 and 15 of Cycle 1,

then on Day 1 of Cycle 2 and beyond. For Cycle 3 and beyond, the interval between blinded study drug and fulvestrant may be adjusted based on the judgment of the investigator.

A cycle is defined as the planned treatment interval of 28 days plus any subsequent delay prior to start of the next cycle. A delay in the start of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 7 days and not counted as a protocol deviation). For each 28-day cycle, a total of 56 doses of blinded study drug will be dispensed. In exceptional cases, for planned delays (including but not limited to vacation or holidays), additional blinded study drug may be dispensed.

A patient may continue to receive study drug(s) until she meets 1 or more of the specified reasons for discontinuation (as described in Section 7.3.1).

9.4.1. Special Treatment Considerations

9.4.1.1. Dose Adjustments and Delays

9.4.1.1.1. Dose Adjustments

9.4.1.1.1.1. Blinded Study Drug

Blinded study drug dose adjustments are allowed both within a cycle and between cycles. Blinded study drug must be reduced as outlined in Table JPBL.9.2.

If a patient who, in the judgment of the investigator, is receiving clinical benefit from study therapy requires further dose reduction than is outlined in Table JPBL.9.2, then the investigator must discuss with the Lilly CRP prior to any further dose reduction.

For patients requiring dose reduction(s), re-escalation to a prior dose level is permitted only after consultation with the Lilly CRP.

Table JPBL.9.2. Dose Adjustments for Blinded Study Drug

Dose Adjustment	Oral Dose	Frequency
0	150 mg	Q12H
1	100 mg	Q12H
2	50 mg	Q12H

In the event that blinded study drug must be discontinued, a patient may continue to receive fulvestrant.

9.4.1.1.1.2. Fulvestrant

Dose adjustment for fulvestrant will be determined by the investigator in accordance with the label. For patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection. In the event that fulvestrant must be discontinued, a patient may continue to receive blinded study drug.

9.4.1.1.2. Dose Delays

The start of a cycle may be delayed up to 14 days to allow sufficient time for recovery from toxicity possibly related to a study drug. During such a delay, blinded study drug and fulvestrant should not be administered. Patients not recovering from toxicity within 14 days beyond the last day of the previous cycle should be considered for dose adjustment or discontinuation of the relevant study drug(s). In exceptional circumstances, a delay >14 days is permitted upon agreement between the investigator and the Lilly CRP.

In the event of a cycle delay due to logistical reasons (for example, due to patient availability), the patient should continue on study treatment if the patient has adequate drug supply. If a patient's treatment is interrupted as a result of not having sufficient drug supply, the cycle may be delayed up to 7 days (and not considered a protocol violation). In exceptional circumstances, a delay >7 days is permitted upon agreement between the investigator and the Lilly CRP.

The start of a cycle may be delayed, or a current cycle interrupted, to allow a patient with a locally advanced breast cancer rendered operable by study treatment to receive surgery ± radiotherapy. For additional information, refer to Section 9.6.1.

9.4.1.1.3. Hematologic Toxicity

If a patient experiences Grade 4 hematologic toxicity possibly related to blinded study drug, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 2) and the dose of blinded study drug must be reduced as outlined in Table JPBL.9.2.

Before the start of each cycle, hematologic toxicity possibly related to blinded study drug must resolve to either baseline or at least Grade 2.

9.4.1.1.4. Nonhematologic Toxicity

If a patient experiences ≥ Grade 3 nonhematologic toxicity possibly related to blinded study drug, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of blinded study drug must be reduced as outlined in Table JPBL.9.2.

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea; refer to Section 9.4.1.1.4.1) possibly related to blinded study drug that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, then dosing may be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of blinded study drug may be reduced as outlined in Table JPBL.9.2.

Before the start of each cycle, nonhematologic toxicity (except alopecia and fatigue) possibly related to blinded study drug must resolve to either baseline or at least Grade 1.

9.4.1.1.4.1. Diarrhea

A patient experiencing diarrhea requiring hospitalization (irrespective of grade, that is, requiring intravenous [IV] rehydration) or severe diarrhea (Grade 3 or 4; see Attachment 9) must have study treatment suspended (until the toxicity resolves to either baseline or at least Grade 1) and must have the blinded study drug dose reduced by one dose level as outlined in Table JPBL.9.2.

If a patient experiences persistent or recurrent diarrhea that does not resolve with maximal supportive measures (refer to Section 9.6.5) within 24 hours so either baseline or at least Grade

1, then study treatment should be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of blinded study drug may be reduced by one dose level as outlined in Table JPBL.9.2 at the discretion of the investigator.

9.5. Blinding

This is a double-blind study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. Access to unblinded data/documents will be controlled by restricting access to the data/documents in Lilly's data and statistical warehouse. Any changes to this unblinding plan may be described in a protocol amendment, the Statistical Analysis Plan (SAP), and/or a separate unblinding plan document.

Efficacy information will not be shared with sites until the study is completed. Upon overall study completion (see Section 8.1.1), investigators may unblind patients to study treatment assignment.

9.5.1. Unblinding at Interim Analyses

Interim analyses for safety and efficacy will be conducted, using unblinded data, under the guidance of an independent Data Monitoring Committee (DMC). The DMC will consist of at least 3 members, including at least 1 clinician and 1 statistician. The DMC will communicate any recommendations based on interim analysis to the Lilly Senior Management Designee (SMD). If necessary, the SMD may form an Internal Review Committee (IRC) to review and act upon the recommendations of the DMC. See Section 12.2.14 for details on the conduct of interim analyses.

9.5.2. Emergency Unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

Emergency unblinding for AEs must be performed through the IWRS. This option may be used ONLY if the patient's acute well-being requires knowledge of the patient's treatment assignment. It is not acceptable to unblind a patient's treatment assignment through direct discussions with unblinded site staff. Every effort should be made to maintain a separation between blinded and unblinded site staff during the course of the study.

All calls resulting in an unblinding event are recorded and reported by the IWRS. If the investigator or patient becomes unblinded, that patient will undergo postdiscontinuation follow-up (Attachment 1).

9.5.3. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator to the identity of the treatment, but the inadvertent unblinding of a patient may occur. A double-blind study design is known to be imperfect in the oncolytic setting because the potential for individual unblinding exists due to treatment-related signs and symptoms. If an investigator, site personnel performing assessments, or patient is unblinded, the unblinding will not be sufficient cause (in and of itself) for that patient to be discontinued from study therapy or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have the patient remain on the study treatment. For patients to continue on study treatment in the event of unblinding, the investigator must obtain specific approval from a Lilly CRP for the patient to continue in the study.

9.6. Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, and concomitant medications must be captured at each visit in the eCRFs and should be recorded throughout the patient's participation in the study. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day short-term follow-up visit.

With the exceptions listed in the sections below, therapies for cancer (including specifically aromatase inhibitors, anti-estrogens other than fulvestrant, chemotherapy, and immunotherapy) will not be permitted while patients are on study treatment. Use of megestrol acetate as an appetite stimulant is not permitted.

The results from an in vitro human recombinant cytochrome P450 (CYP) phenotyping study indicate that oxidative metabolism of abemaciclib is primarily catalyzed by CYP3A4. However, the extent of oxidative metabolism responsible for the systemic clearance of abemaciclib in humans is presently unknown. Based on these in vitro findings, grapefruit juice as well as inducers (for example, phenytoin or carbamazepine) and strong inhibitors of CYP3A4 should be substituted or avoided if possible (Attachment 8). In addition, in vitro studies in primary cultures of human hepatocytes indicate that abemaciclib might inhibit the metabolism of CYP2B6 substrate drugs in vivo in humans. Based on this finding, bupropion and efavirenz, which are sensitive CYP2B6 substrates, should be substituted or avoided if possible.

9.6.1. Surgery and/or Radiotherapy for Locally Advanced Breast Cancer

A patient with locally advanced breast cancer may receive surgery ± radiotherapy if study treatment renders the tumor operable. However, such a patient should not receive study treatment for the period beginning at least 7 days prior to surgery and continuing until at least 14 days after completion of surgery ± radiotherapy to allow for tissue healing and recovery. There is no restriction on the duration of this period without study treatment and, after this period ends, study treatment and protocol procedures (Attachment 1) should either resume based upon the most recent cycle completed prior to surgery ± radiotherapy or the patient should be discontinued from study treatment. Importantly, a patient who receives surgery ± radiotherapy

for locally advanced breast cancer is not considered noncompliant and does not incur a protocol deviation.

9.6.2. Radiotherapy

Except as described in Section 9.6.1, radiotherapy is not permitted without permanent discontinuation from study treatment. Except for a patient with locally advanced breast cancer rendered operable by study treatment who subsequently undergoes surgery + radiotherapy, all other patients requiring radiotherapy should discontinue permanently from study treatment and have a tumor assessment of the lesion(s) before receiving radiotherapy.

9.6.3. Supportive Care

Patients should receive full supportive care to maximize quality of life. Patients will receive supportive care as judged by their treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP. Use of any supportive care therapy should be reported in the eCRFs.

9.6.4. Growth Factors

Growth factors may be administered in accordance with ASCO guidelines (Smith et al. 2006; Rizzo et al. 2008).

9.6.5. Supportive Management for Diarrhea

At randomization, patient should receive instructions on the management of diarrhea. In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (e.g. loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours
- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours to either baseline or Grade 1, blinded study drug should be suspended until diarrhea is resolved to baseline or Grade 1.
- When blinded study drug recommences dosing should be adjusted as outlined in Section 9.4.1.1.1.1 and Table JPBL.9.2.

In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

Patients with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid (IV hydration) and electrolyte replacement.

9.6.6. Bisphosphonates and RANK-L Targeted Agents

Use of bisphosphonates or approved RANK-L targeted agents (for example, denosumab) is permitted during participation in the study. Patients should if possible begin treatment with bisphosphonates or RANK-L targeted agents before or concurrently with initial study treatment. Patients who start the study receiving bisphosphonates or RANK-L targeted agents should, if possible, avoid switching treatments (for example, replacing a bisphosphonate with denosumab) while on study treatment. After study treatment discontinuation, use of bisphosphonates or RANK-L targeted agents is at the discretion of the treating physician.

9.6.7. Ovarian Suppression with Gonadotropin-Releasing Hormone Agonists

Patients who are postmenopausal due to ovarian suppression should, if possible, continue GnRH agonist therapy during study treatment.

9.7. Treatment Compliance

Treatment compliance information for study drugs will be collected through counts at each visit, and the number of capsules taken relative to the number expected to be taken will be summarized for each cycle. The patient must take ≥75% of the planned doses for assigned study drug in a cycle to be deemed compliant. Similarly, a patient may be considered noncompliant if she is judged by the investigator to have intentionally or repeatedly taken ≥125% of the planned doses of study drug in a cycle.

Importantly, a patient who receives surgery ± radiotherapy for locally advanced breast cancer is not considered noncompliant and does not incur a protocol deviation. For additional information, refer to Section 9.6.1.

Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP or clinical research scientist before any determination is made to discontinue the patient.

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Written informed consent must be obtained prior to any study-specific pretreatment evaluations.

Study procedures related to efficacy, safety, health outcome/quality of life measures, sample collection, and testing assessments and their timing are described in the sections below and shown in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Efficacy Assessments at Baseline and during Study Treatment

Within 28 days of randomization, baseline tumor measurements will be performed on each patient. Computed tomography (CT), including spiral CT, scans and magnetic resonance imaging (MRI) are the preferred methods of measurement. In addition, bone scintigraphy will be performed for all patients at baseline (within 28 days of randomization). However, prior bone scintigraphy (obtained as part of routine clinical care) within 45 days before Day 1 of Cycle 1 is also acceptable. *For only those patients with bone lesions identified by bone scintigraphy at baseline,* all such lesions will be evaluated at baseline by focused studies (X-ray, CT scan with bone windows, or MRI) to enable serial assessment. *For patients with inoperable locally advanced breast cancer,* MRI scan of the breast will be performed at baseline. *For patients with visible tumor (such as skin lesions),* photography will be performed at baseline and each photographic image of the tumor should include a ruler.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast). A PET scan alone or as part of a PET-CT scan may be performed separately as part of routine clinical care but cannot be used to assess response according to RECIST v1.1.

The methods of assessment used at baseline must be used consistently for tumor assessment and will be repeated (with the exception of bone scintigraphy) between Day 1 and Day 7 of every second cycle beginning with Cycle 3 and continuing through Cycle 13 (inclusive), between Day 1 and Day 7 of every third cycle after Cycle 13, and within 14 days of clinical progression. For assessment of response *only in patients with bone lesions identified by scintigraphy at baseline*, the method of assessment used at baseline (X-ray, CT scan with bone windows, or MRI) will be repeated between Day 1 and Day 7 of every second cycle beginning with Cycle 3 and continuing through Cycle 13, between Day 1 and Day 7 of every third cycle after Cycle 13, and within 14 days of clinical progression. Bone scintigraphy should be repeated for all patients between Day 1 and Day 7 of every sixth cycle beginning with Cycle 7, when complete response is identified in target disease, or when progression in bone is suspected. For patients with new lesions identified by post-baseline bone scintigraphy, targeted assessment by X-ray, CT scan

with bone windows, or MRI will be performed to confirm findings as described in the Study Schedule (Attachment 1).

Responses (CR or PR) must be confirmed no less than 28 days from the first evidence of response.

For patients continuing treatment after study completion, efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator.

10.1.2. Efficacy Assessments during the Study Period Postdiscontinuation Follow-Up

Postdiscontinuation follow-up during the study period will be conducted as described in the Study Schedule (Attachment 1).

For those patients who discontinue study treatment without objectively measured progressive disease (PD), the investigative sites will continue to monitor patients and periodically evaluate tumor response approximately every 8 weeks for the first 12 months following randomization and thereafter approximately every 12 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression, or until the primary analysis of PFS. After the patient has objective disease progression, radiologic tests are no longer required and the patient will be followed up approximately every 12 weeks (± 14 days) until the patient's death or overall study completion.

After study completion, efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator.

10.1.3. Primary Efficacy Measure

The primary efficacy measure is progression-free survival as defined by RECIST Version 1.1 (Eisenhauer et al. 2009) provided in Attachment 5.

Lilly or its designee will collect and store all tumor measurement images on all enrolled patients throughout the study. An independent review of imaging scans will be performed by an independent panel of radiologists.

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.

For those patients with nonmeasurable, bone only disease (refer to Inclusion Criterion [5]), objective progression will be established if at least 1 of the following criteria is met:

- the appearance of 1 or more new lesions (in bone or outside of bone), or
- unequivocal progression of existing bone lesions.

Pathologic fracture, new compression fracture, or complications of bone metastases will not be considered as evidence of disease progression, unless at least 1 of the above criteria is met.

For those patients with locally advanced disease for whom surgery is performed with no evidence of residual disease post-operatively, objective progression will be established if at least 1 of the following criteria is met:

- local recurrence, or
- new development of metastatic disease.

For those patients with locally advanced disease for whom surgery is performed with evidence of residual disease post-operatively, new baseline measurements should be taken and RECIST applied.

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. See Section 12.2.6 for detailed censoring rules.

10.1.4. Secondary Efficacy Measures

The following secondary efficacy measures (Table JPBL.10.1) will be collected at the times shown in the Study Schedule (Attachment 1).

Table JPBL.10.1. Secondary Efficacy Endpoints

Endpoint	Definition
Overall Survival (OS)	The time from the date of randomization to the date of death from any cause
Objective Response Rate	The proportion of patients with CR or PR according to RECIST v1.1
Disease Control Rate (DCR)	The proportion of patients with CR, PR, or SD according to RECIST v1.1
Duration of Response (DoR)	The time from the date of first evidence of a confirmed CR or PR to the date of objective progression or death from any cause, whichever is earlier
Time to Worsening ECOG Performance Status (PS)	The time from the date of randomization to the date of first PS ≥2
Time to First Skeletal-Related Event (TTFSRE)	The time from the date of randomization to the date of first: • Spinal cord compression OR • Pathological fracture OR • Radiation to bone OR • Surgery to bone

Abbreviations: CR = complete response; PR = partial response; PS = performance status; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

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).

Objective Response Rate: The objective response rate is the percentage of patients with a best response of CR or PR.

Duration of Response (DoR): The DoR time is defined only for responders (patients with a confirmed 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. For clarity, the start date should be determined by the initial assessment of CR or PR, not the date of confirmation of CR or PR. If a responder is not known to have died or have objective progression as of the data inclusion cutoff date scores, duration of response will be censored at the last complete objective progression-free disease assessment date.

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

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

Time to First Skeletal-Related Event (TTFSRE): Patients will be monitored for development of SREs at each cycle. An SRE will be defined as any of the following: spinal cord compression, pathological fracture, radiation to bone, or surgery to bone. The anatomic location, days of hospitalization, relatedness to breast cancer, and procedure(s) used for treatment will be captured. Bone survey will be monitored according to the Study Schedule (Attachment 1).

TTFSRE and a comparison of the frequency of SREs between treatments will be conducted at the end of the study. TTFRSE is defined as the time from randomization to documentation of the first postbaseline occurrence of any SRE. Patients not known to have had an SRE at the time of the analysis will be censored at the date of their last complete documented assessment for SRE.

SRE-specific information should be collected until patient death, loss to follow-up, or study completion.

Time to Worsening ECOG Performance Status: will be defined as the time from randomization to an ECOG performance status evaluation of 2 or worse. Patients with no evaluation of 2 or worse will have their time to deterioration of performance status censored at the date of the last performance status evaluation.

10.1.5. Exploratory Efficacy Measures

Time to Progression of Bone Metastases	The time from the date of randomization to the date of earliest development of new bone metastases

10.2. Health Outcome/Quality of Life Measures

10.2.1. Patient-Reported Outcomes

The primary health outcomes research goal is to determine if abemaciclib combination therapy is able to palliate pain, as measured by the mBPI-sf (Cleeland 1991). Additionally, the EORTC QLQ-C30 (Aaronson et al. 1993) will assess the broader impact of abemaciclib combination therapy on quality of life, the EORTC QLQ-BR23 (Sprangers et al. 1996) will collect disease-specific data, and the EQ-5D 5L (Janssen et al. 2008) health status assessment will allow for comparison with other tumor types and disease states.

Patient-reported questionnaires should be completed by patients when a language translation is available in which the patient is fluent or literate.

At each time point identified in the Study Schedule (Attachment 1), a paper copy of the mBPI-sf, EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D 5L questionnaires should be administered to the patient prior to extensive interaction with site staff and study drug administration.

10.2.1.1. Pain Intensity

The mBPI-sf (Cleeland 1991) is an 11-item instrument used as a multiple-item measure of cancer pain intensity. In addition to pain intensity (4 items), the mBPI-sf is designed for patients to record the presence of pain in general, pain relief, and pain interference with function (general activity, mood, ability to walk, ability to perform normal work, relations with others, sleep, and enjoyment of life).

Responses for the mBPI-sf items are captured through the use of 11-point numeric rating scales anchored at 0 (*no pain* or *does not interfere*) and ranged through 10 (*pain as bad as you can imagine* or *completely interferes*). The mBPI-sf recall period is 24 hours, and pain relief is assessed with a scale range from 0% (*no relief*) through 100% (*complete relief*). Typical completion time for this instrument is less than 5 minutes. Focused analysis will be on "worst pain".

Use of pain medication will be assessed in conjunction with the mBPI-sf assessment. Data on each individual prescription and over-the-counter analgesic medication will be recorded on the Concomitant Medications eCRF. The use of pain medications should be reviewed with the patient at each subsequent visit. Any changes to analgesic use (new or stopped analgesics) will be recorded on the eCRF. Pain medication will be classified into 1 of 6 categories, using an analgesic ladder approach with medication category based on a World Health Organization scale outlined in Table JPBL.10.2. A therapy category will be assigned according to the maximum category of therapy administered based on analgesic data for that cycle. Category of pain medication for each cycle will be determined based on the data collected on analgesic use by Anatomical Therapeutic Chemical code.

The BPI population will include all patients who completed at least 1 baseline followed by at least 1 BPI "worst pain" assessment after 1 cycle of study drug (Cycle 2 Day 1 or later).

Table JPBL.10.2. World Health Organization Pain Scale

Code	Description
0	No analgesia
1	Aspirin (for pain, not cardiovascular prophylaxis), acetaminophen, nonsteroidal anti-inflammatory drugs
2	Codeine, hydrocodone, pentazocine, oxycodone
3	Oral morphine, hydromorphone, methadone, transdermal fentanyl
4	Parenteral opiates
5	Neurosurgical procedures (blocks)

10.2.1.2. Health-Related Quality of Life

Broadly used in cancer trials, validated, and available in over 80 different languages, the EORTC QLQ-C30 (Aaronson et al. 1993) is a reliable and validated tool that has supported quality-of-life

claims in both Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMA) labels. The EORTC QLQ-C30 self-reported general cancer instrument (Aaronson et al. 1993) consists of 30 items covered by 1 of 3 dimensions:

- global health status/quality of life (2 items)
- functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning)
- symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact)

The EORTC QLQ-BR23 (Sprangers et al. 1996) consists of 23 items covered by the following scales:

- functional (body image and sexuality)
- symptom scales (arm, breast, and systemic therapy side effects)

The EORTC QLQ-C30 and EORTC QLQ BR23 questionnaires are administered per the Study Schedule (Attachment 1). The recall period is the past week, completion time is typically 5 to 7 minutes, and both questionnaires will be scored as described by the EORTC scoring manual (Fayers et al. 2001). The EORTC population will include all patients who completed at least 1 baseline followed by at least 1 EORTC assessment after 1 dose of study drug (Cycle 2 Day 1 or later).

10.2.1.3. Health Status

The EQ-5D 5L (Janssen et al. 2008) is a standardized instrument for use across diseases as a measure of self-reported health status. Specifically, this questionnaire is included in this trial to evaluate health-state utilities associated with advanced breast cancer. These utility measures are an important input for economic evaluations concerning the value of treatment interventions.

The EQ-5D 5L is designed to be used in conjunction with other patient-reported measures. Patients will complete the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment according to the Study Schedule (Attachment 1). A visual analog scale (VAS) "thermometer" measures current health state.

Administration is preferably scheduled after the BPI and the EORTC, and before extensive contact with study personnel or clinicians, which could result in biased patient response. The recall period is “today.” The EQ-5D 5L is designed for self-completion by respondents and is cognitively simple, taking only a few minutes to complete.

The EQ-5D 5L population will include all patients who completed at least 1 baseline followed by at least 1 EQ-5D 5L assessment after 1 dose of study drug.

10.2.2. Resource Utilization

Investigators will be asked to report the use of concomitant medications (in particular, analgesics, bisphosphonates, and RANK-L targeted agents), blood product transfusions, radiation therapy, surgery, and hospitalization days. Data on neurosurgical blocks will be

recorded on the Concomitant Medication and/or surgery eCRF as appropriate. This information should be collected during the study and at the 30-day follow-up visit.

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JPBL.10.3 presents a summary of AE and SAE reporting guidelines. Table JPBL.10.3 also shows which database or system is used to store AE and SAE data.

Table JPBL.10.3. Adverse Event and Serious Adverse Event Reporting Guidelines

Period	Types of AEs/SAEs to be Reported	Collection Database	Lilly Safety System
Baseline (pretreatment)	Preexisting conditions	x	
	All AEs	x	
	SAEs related to protocol procedures	x	x
Study treatment period	All AEs	x	
	All SAEs	x	x
30-day short-term postdiscontinuation follow-up	All AEs	x	
	All SAEs	x	x
Long-term postdiscontinuation follow-up	All SAEs related to protocol procedures or study drug or drug delivery system	x	x
Extension period	All AEs	x	
	All SAEs	x	x
Extension period follow-up	All AEs	x	
	All SAEs	x	x
After the patient is no longer participating in the study (that is, no longer receiving study therapy and no longer in follow-up)	All SAEs related to protocol procedures or study drug or drug delivery system that the investigator becomes aware of		x

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

10.3.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to that drug or drug delivery system.

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Any clinically significant findings from electrocardiograms (ECGs), labs, vital sign measurements, and other procedures that result in a diagnosis should be reported to Lilly or its designee.

Cases of pregnancy that occur during maternal exposures to study drug should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record the occurrence and nature of any AEs and any change in the preexisting condition(s). All AEs related to protocol procedures are reported to Lilly or its designee.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure and study drugs via eCRF.

The investigator will decide whether he or she interprets the observed AEs as related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug or procedure, the following terminologies are defined:

- **Probably related**: a direct cause and effect relationship between the study treatment and the AE is likely
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible
- **Does not know:** the investigator cannot determine
- **Not related**: without question, the AE is definitely not associated with the study treatment

The investigator should classify all "probably related," "possibly related," or "does not know" AEs and SAEs as related to study drug/study procedure.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

The NCI-CTCAE v 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI-CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim and the CTCAE severity grade, AE verbatim text will also be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA®).

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.3.1.1. Serious Adverse Events

An SAE is any adverse event from this study that results in one of the following outcomes:

- death
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- initial or prolonged inpatient hospitalization
- 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 serious adverse drug events when, based upon 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.

Serious adverse event collection begins after the patient has signed informed consent and has received study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will not be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

Study site personnel must alert Lilly or its designee of any **serious** adverse event (SAE) within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms.

This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

Serious adverse events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug.

When a condition related to the prefilled fulvestrant syringes necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned on the eCRF.

If an investigator becomes aware of an SAE occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure, a study drug, or prefilled fulvestrant syringes, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.3.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Development Core Safety Information in the IB and that the investigator identifies as related to the study drug or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

10.3.2. Other Safety Measures

10.3.2.1. Electrocardiograms

For each patient, a local 12-lead digital ECG will be collected according to the Study Schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, if clinically indicated.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/corrected QT interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, or syncope) and to determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

10.3.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP will, as is appropriate, consult with the functionally independent GPS therapeutic area physician or clinical scientist, and review:

- trends in safety data
- laboratory analytes
- adverse events
- If a patient experiences elevated ALT ≥ 5 times ULN and elevated total bilirubin ≥ 2 times ULN, clinical and laboratory monitoring should be initiated by the investigator.
- Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specifically recommended clinical information and follow-up laboratory tests. See Attachment 3.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the DMC (an advisory group for this study formed to protect the integrity of data; refer to Section 12.2.14) can conduct additional analyses of the safety data.

For the purpose of this study, in which survival is a key efficacy endpoint, all deaths and SAE reports will be reviewed in a blinded manner by Lilly during the clinical trial. These reports will be reviewed to assure completeness and accuracy but will not be unblinded to Lilly during the clinical trial. If a death or other clinical AE is deemed serious, unexpected, and possibly related to study drug, only Lilly GPS representatives external to the study team will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this trial and minimize any potential for bias while providing for appropriate safety monitoring.

10.3.4. Complaint Handling

Lilly collects product complaints on study drugs and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to fulvestrant or the prefilled fulvestrant syringes should be reported directly to the manufacturer in accordance with the package insert.

Complaints related to blinded study drug should be reported directly to Lilly.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.4. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study and whether these will be performed at a central or local laboratory.

Attachment 6 provides a summary of the estimated maximum number and volume of invasive samples, for all sampling, during the study.

Attachment 7 lists the schedule for PK sampling during the study.

10.4.1. Samples for Study Qualification and Health Monitoring

Blood samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol deviations.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.4.2. Samples for Tailoring Biomarkers

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis.

Samples for biomarker research to be collected from all patients in this study:

- blood
- tumor tissue

Analyses may include, but are not limited to, nucleic acid and protein profiles to better understand the disease process and to develop predictive biomarkers.

These samples are described in the following sections.

10.4.2.1. Archived Tumor Tissue

For patients in the study, a small amount of preserved tumor tissue, previously taken to evaluate the patient's disease, should be requested for biomarker research. Formalin-fixed paraffin-

embedded tumor tissue should be in a whole block, partial block, or unstained slides. Any whole block submitted will be returned to the site. Any partial blocks or slides will either be returned or discarded within 15 years after last patient visit for the trial.

In tumor tissue samples, the CDK4/6 pathway components (for example, Rb) and markers relevant breast cancer pathogenesis may be evaluated to assess any potential correlation with response to abemaciclib. Tumor samples may be analyzed to explore potential tumor gene signature(s) associated with response or resistance to abemaciclib therapy. These studies may be analyzed at a laboratory designated by the sponsor and may include IHC of proteins, FISH for copy number amplifications, RNA gene-expression profiling, and/or genetic analyses of the tumor specimen DNA. Such analyses may employ targeted or high-throughput sequencing approaches. For this purpose, the results of this analysis will be correlated with clinical efficacy data.

10.4.2.2. Blood Samples for Pharmacogenetic Evaluations

Where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis. Samples may be genotyped and analysis may be performed to evaluate a genetic association with response to abemaciclib. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Samples will be destroyed according to a process consistent with local regulation.

10.4.2.3. Plasma Samples for Exploratory Biomarker Evaluations

Plasma samples will be collected and analysis may be performed on biomarkers that may play a role in the abemaciclib mechanism of action (refer to Attachment 1). The evaluation of these samples may involve analysis of DNA, RNA, and proteins (including any of these components derived from exosomes) to investigate their association with observed clinical outcomes to study drug. The samples will be coded with the patient number and stored for up to a maximum 15 years. Details for collecting, processing, and storing the samples are similar those provided in Section 10.4.2.2.

10.4.3. Samples for Drug Concentration Measurements Pharmacokinetics

At the visits and times specified in the Pharmacokinetic Sampling Schedule (Attachment 7), venous blood samples of approximately 4 mL each will be collected to determine the plasma

concentrations of abemaciclib and its metabolites LSN2839567, LSN3106726, and LSN3106729, as well as plasma concentrations of fulvestrant.

Separate blood samples are not required for the parent, its metabolites, and fulvestrant. After obtaining plasma, samples will be aliquoted into 2 approximately equal portions by site personnel, one for the determination of plasma concentrations of abemaciclib and its metabolites and the other for the determination of plasma concentrations of fulvestrant. Instructions for the collection and handling of blood samples will be provided by the sponsor. It is preferred that the blood samples be obtained from a peripheral location. Blood samples will be allowed from central access devices, but a sample drawn from a central catheter of any type for PK must take precautions to prevent obtaining a dilute sample. If multiple samples are obtained centrally, the PK sample should be the last specimen drawn to reduce the potential for a diluted or improperly drawn sample. The actual date and time (24-hour clock time) of each sampling will be recorded. A maximum of 5 samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and Lilly.

These samples will be analyzed at a laboratory designated by the sponsor. Plasma concentrations of abemaciclib plus its metabolites LSN2839567, LSN3106726, and LSN3106729 will be assayed using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method. Plasma concentrations of fulvestrant will also be analyzed using a validated LC/MS/MS method. Bioanalytical samples collected to measure study drug concentration and metabolism and/or protein binding, will be retained for a maximum of 1 year following last patient visit for the study. The PK samples will be stored at a facility designated by the sponsor.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

10.5. Appropriateness of Measurements

Efficacy measurements by radiographic imaging are standard, widely used, and generally recognized as reliable, accurate, and able to discriminate between effective and ineffective agents.

Safety measurements by laboratory monitoring are standard, widely used, and generally recognized as reliable, accurate, and able to discriminate between agents with acceptable and unacceptable safety profiles.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this trial. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly generic labs system.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

The primary objective of this study is to compare abemaciclib plus fulvestrant versus placebo plus fulvestrant in terms of PFS for women with HR+, HER2- locally advanced or metastatic breast cancer.

The study will enroll approximately 550 patients in 2:1 randomization. Patients will be randomized using the following stratification factors: nature of disease (visceral metastases versus bone only metastases versus other) and sensitivity to endocrine therapy (no prior endocrine therapy versus primary resistance versus secondary resistance).

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 Section 12.2.6 for details). The primary PFS analysis will be performed after 385 PFS events have occurred (that is, a 30% censoring rate). Assuming a hazard ratio (HR) of 0.703, this sample size yields at least 90% statistical power to detect superiority of the abemaciclib plus fulvestrant arm over the placebo plus fulvestrant 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 fulvestrant arm is 6.5 months, then the HR of 0.703 amounts to an approximately 2.75-month (42%) improvement in median PFS for the abemaciclib plus fulvestrant arm under an additional assumption of exponential survival distribution. Assuming approximately 10% screening failure, the study will enter approximately 600 patients.

OS is an important secondary endpoint for this study. OS will be tested only if the test of PFS is significant. A 4-look approach to testing OS with a cumulative 1-sided type I error rate of 0.025 will be utilized to allow for analyses of OS at: the interim PFS analysis, the primary PFS analysis, 289 OS events, and the final OS analysis at 385 OS events (see Section 12.2.7 for details).

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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

Efficacy analyses will be based on the intention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. Patients will be grouped according to randomized treatment.

Safety analyses will be based on the Safety Population, defined as all enrolled patients receiving at least 1 dose of blinded study drug or fulvestrant. Patients will be grouped according to treatment received in Cycle 1.

Pharmacodynamic and/or tailoring 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.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All tests of interactions will be conducted at a 2-sided alpha level of 0.1, and all confidence intervals (CIs) will be given at a 2-sided 95% level, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol.

Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the statistical analysis plan.

Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

The assumptions for each statistical method will 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.

12.2.2. 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, and treated, as well as number and percentage of patients completing the study or discontinuing (overall and by reason for discontinuation).

All patients entered in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins will be specified.

A summary of all important protocol deviations will be provided.

12.2.3. Patient Characteristics

Patient characteristics will include a summary, by treatment arm, of the following:

- patient demographics
- baseline disease characteristics
- preexisting conditions
- historical illnesses
- prior endocrine therapy
- prior chemotherapy (including both cytotoxic and targeted agents)

Other patient characteristics will be summarized as deemed appropriate.

12.2.4. Concomitant Therapy

Concomitant medication will be summarized by treatment arm in a frequency table listing the terms recorded on the eCRF.

12.2.4.1. Postdiscontinuation Therapy

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

12.2.5. Treatment Compliance

The number of dose omissions, reductions, and delays, cycles received, and dose intensity will be summarized for all treated patients per treatment arm.

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

$$\text{Percent Compliance} = \frac{\text{Actual cumulative dose taken}}{\text{Expected cumulative dose to be taken}} \text{ x } 100$$

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. The expected cumulative dose to be taken will be determined based on the assigned dose and taking into account any dose reductions or omissions.

12.2.6. Primary Outcome and Methodology

The primary endpoint of this study is PFS. PFS time is measured from the date of randomization to the date of investigator-determined objective progression as defined by RECIST v1.1, or death from any cause. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment (if available) or date of randomization if no post initiation (that is, postbaseline) radiographic assessment is available. The detailed censoring rules are described below (Table JPBL.12.1).

Table JPBL.12.1. 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 ≥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.

The PFS analysis to test the superiority of abemaciclib to placebo in improving PFS time will use the log-rank test stratified by nature of disease (visceral metastases versus bone only metastases versus other) and sensitivity to endocrine therapy (no prior endocrine therapy versus primary resistance versus secondary resistance). In addition, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the PFS curves as well as PFS rates at every 3 months for each treatment group. These rates will be compared based on a normal approximation for the difference between the rates.

The 2-look group-sequential design of the primary endpoint will be used to accommodate an event-driven plan for the interim and primary analysis. There is 1 planned interim analysis and 1 primary analysis for PFS in this study. The interim analysis is planned to take place after approximately 270 (70%) investigator-assessed PFS events have occurred. The cumulative 1-sided type I error rate of .025 will be maintained using the Lan-Demets method. Specifically, an α-spending function corresponding to an O'Brien-Fleming type stopping boundary (as implemented in ADDPLAN 6.0) will be used for this interim efficacy analysis:

$$\alpha^*(t_k) = 2\left(1 - \Phi\left(\Phi^{-1}(1-\alpha/2) \Big/ \sqrt{t_k}\right)\right).$$

Here, t_k is the information fraction at time k, Φ is the standard normal cumulative distribution function, and Φ^{-1} is the standard normal quantile function.

Therefore, if the interim analysis is performed after exactly 270 events have been observed, a nominal 1-sided p-value of less than 0.0074 (corresponding approximately to an observed HR <0.73 under an exponential model) will need to be observed to declare statistical significance (see Table JPBL.12.2).

Table JPBL.12.2. Property of the Design for Progression-Free Survival

Information Fraction	Cumulative Events	Cumulative Alpha Spent	Cumulative Beta Spent	Boundary Reject H_0 (1-sided p-value)
0.7	270	0.0074	0	<.0074
1	385	0.025	0.1	<.0228

Abbreviation: H_0 = null hypothesis.

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 statistical significance is not declared at the interim PFS analysis, the primary PFS analysis will be performed after 385 PFS events have been observed based on investigator assessment. The primary PFS analysis will compare 2 treatment groups using a log-rank test stratified by the randomization factors.

The Cox proportional hazard model (Cox 1972) with treatment as a factor will be used to estimate the HR and corresponding 95% CI with Wald's test p-value after adjusting for the same randomization variables specified for the primary analysis. All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint. An additional unstratified Cox regression model will be employed to explore the effects of prognostic variables, such as of the stratification variables and intrinsic/extrinsic factors, on treatment response.

12.2.7. Secondary Outcome and Methodology

The secondary objectives of the study are to:

- compare the following efficacy endpoint between treatment arms:
  - overall survival (OS)
  - OS at 1, 2, and 3 years
  - objective response rate (CR + PR)
  - duration of response (CR + PR)
  - disease control rate (DCR) (CR + PR + stable disease SD)
  - clinical benefit rate (CBR) (CR + PR + SD ≥6 months)
- compare AEs between treatment arms

- compare pain and symptom burden between treatment arms using the BPI, EORTC QLQ-C30, EORTC QLQ-BR23, and health status using the EQ-5D 5L

OS is an important secondary endpoint for this study. OS will be tested only if PFS is significant. Up to a total of 3 interim analyses and a final analysis for OS may be performed in this study. The interim analyses on OS will occur at the interim PFS analysis, the primary PFS analysis, and when 289 OS events have been observed. The final OS analysis will be performed after 385 OS events have occurred. The type I error rate will be controlled at 2.5% by using a 4-look Lan-Demets design with an O'Brien-Fleming type stopping boundary (using the same spending function as described for PFS). 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). Table JPBL.12.3 summarizes expected OS events, critical boundary, and cumulative alpha spending for OS analysis. The exact nominal p-values required to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of each analysis.

Table JPBL.12.3. Property of the Design for Overall Survival

Time Point	Expected Information Fraction	Cumulative Events	Cumulative Alpha Spent	Boundary Reject H_0 (1-sided p-value)
Interim PFS	0.25	96	0.00001	<0.00001
Primary PFS	0.50	193	0.00153	<0.00152
289 OS Events	.75	289	0.00965	<0.00916
385 OS Events	1	385	0.025	<0.02200

Abbreviations: H_0 = null hypothesis; OS = overall survival; PFS = progression-free survival.

To maintain the experiment-wise type I error rate, OS will be hierarchically tested in the following way: only if the test of PFS is significant will OS also be tested inferentially for significance (Glimm et al. 2010); specifically:

- The first potential time point for OS analysis will be at the time of the PFS interim analysis. If PFS is significant at this stage, the first interim analysis of OS will also be performed. If OS is not significant at this stage, the second interim analysis of OS will be performed after 193 deaths. If OS is not significant at this stage, a third interim analysis of OS will be performed after 289 deaths. If OS is not significant at this stage, a final analysis will be performed after 385 deaths have been recorded.
- If PFS is not significant at the time of the interim analysis of PFS but is significant at a primary analysis for PFS, the second interim analysis of OS will be performed. In terms of alpha spending, this analysis will be performed as if an analysis of OS had occurred at the interim PFS analysis. If OS is not significant at this stage, the next analysis on OS will be performed when a total of 289 deaths have been recorded. If OS is not significant at this stage, a final analysis will be performed after 385 deaths have been recorded.

- If PFS is not significant after the primary analysis for PFS is performed, OS will not be statistically evaluated.

The OS analysis to test the superiority of abemaciclib to placebo in improving OS time will use the log-rank test stratified by nature of disease (visceral metastases versus bone only metastases versus other) and sensitivity to endocrine therapy (no prior endocrine therapy versus primary resistance versus secondary resistance).

The following additional analyses will be conducted for OS:

- Kaplan-Meier curves (Kaplan and Meier 1958) will be generated; medians, quartiles, and appropriate point probabilities will be calculated. Interval estimates will be calculated using 95% CI.
- The Cox regression stratified by the randomization factors will be used to estimate the HR between the 2 treatment groups, along with 95% CI.

In addition, OS rate at 1 year in each treatment arm will be calculated by determining OS time for each patient and using Kaplan-Meier techniques to assess OS time for each treatment arm. The Kaplan-Meier estimate of the OS rate at 1 year will be used to compare treatment arms using a standard normal test of the difference in OS rate at 1 year. The same techniques will be used to calculate and compare OS rates at 2 years and 3 years between arms.

The objective response rate, DCR, and CBR of each treatment arm will be calculated as defined by RECIST v1.1. All rates will be compared between treatment arms based on a normal approximation for the difference between the rates.

12.2.8. Sensitivity Analysis

Sensitivity analyses will be undertaken for calculation of the primary endpoint in order to evaluate the robustness of the analysis. The following sensitivity analyses will be performed for PFS:

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 (censoring for study treatment discontinuation due to toxicity): if a patient is discontinued from study treatments due to toxicity prior to objective progression, then the PFS time will be censored at the last complete objective progression-free disease assessment date prior to the discontinuation, regardless of whether or not this patient subsequently had objective progression or died.

Progression-Free Survival Sensitivity Analysis 3 (censoring for any of above situations): if a patient has any of the following situations outlined for sensitivity analyses 1 through 2 prior to objective progression, then the PFS time will be censored at the last objective progression-free

disease assessment date prior to the earliest occurrence of any of these situations, regardless of whether or not this patient subsequently had objective progression or died.

Progression-Free Survival Sensitivity Analysis 4 (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 5 (back-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 back-dated to the prior scheduled disease assessment.

In addition, a PFS analysis based on independent central review data will be conducted by applying the censoring rules from Table JPBL.12.1. The analysis will be conducted on a randomly selected subset of patients to evaluate the presence of investigator bias with the intention of evaluating the reliability of the treatment effect based on investigator assessment. Dodd (Dodd et al. 2011), Pharmaceutical Research and Manufacturers Association (PhRMA) methodology (Amit et al. 2011), or similar methodology will be used to determine audit size and evaluate the results and determine whether independent review of the remaining patients is warranted. Details can be found in the SAP.

An additional OS analysis will also be conducted based on the following definition using similar methods as stated in Section 12.2.7: time is defined as the time from the date of study enrollment to the date of death due to disease. Survival time will be censored on the date the patient was last known to be alive for patients who have no reported event. For patients that have died due to reasons not disease related, survival time will be censored at the date of death.

12.2.9. Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetics analyses will be conducted on all patients who have received at least 1 dose of abemaciclib and have had samples collected (see PK sampling schedule in Attachment 7).

Mean population PK parameters for abemaciclib and its metabolites in plasma (clearance, exposure, volume of distribution, and half-lives) and inter-individual PK variability will be computed using nonlinear mixed effect modeling implemented in NONMEM. The current PK model for abemaciclib, which has been developed using plasma concentration data available from the Phase 1 Study JPBA, will be updated using the plasma data collected in this study. Covariate effects (such as age, weight, sex, creatinine clearance, and plasma protein levels) on the PK parameters of abemaciclib in plasma will also be investigated.

If warranted by the data, mean population PK parameters for fulvestrant in plasma and inter-individual variability estimates will also be computed using nonlinear mixed effect modeling implemented in NONMEM.

Finally, pharmacodynamic data (such as neutrophil, lymphocytes, or platelets counts in blood) collected in this study may be analyzed by means of NONMEM and connected to the population PK model for abemaciclib and/or fulvestrant in a PK/pharmacodynamic model.

The version of software used for the analysis will be documented and will meet the Lilly requirements of software validation.

12.2.10. Tailoring Biomarker Analyses

The distributions of biomarkers with continuous measures, such as gene or protein expression, will be described. Summary statistics will include means, medians, corresponding standard errors, quartiles, and ranges. Biomarkers with discrete measures, such as genotype locus, will be summarized in frequency tables. Correlative analyses may be performed to investigate associations between biomarkers and clinical endpoints as deemed appropriate.

12.2.11. Health Outcome/Quality of Life Analyses

Patient-reported outcomes are measured through paper versions of the following:

- mBPI-sf (modified Brief Pain Inventory, Short Form)
- EORTC QLQ-C30 (The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30)
- EORTC QLQ-BR23 (The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast cancer)
- EQ-5D 5L (EuroQol 5-Dimension 5 Level)

For each patient with data from baseline and at least 1 other visit, the maximum change from baseline score will be calculated and summarized for BPI "worst pain", EORTC composite scores. The reason and number of missing and incomplete questionnaires/assessments by visit will be summarized for each instrument and study arm.

Exploratory analysis may be performed to investigate associations between patient-reported data (BPI, EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D) and additional clinical, efficacy, and /or utilization measures as appropriate.

Additionally, exploratory joint-modeling analyses may be conducted to identify composite patient-reported outcome (PRO) scores or single items that are related to survival or response. This exploratory analysis may include one or more of the patient-reported instruments (see Section 10.2).

Further analysis details will be described in the SAP.

12.2.11.1. Pain Intensity

Individual pain items on the mBPI-sf (that is, worst, least, average, and current pain) will be described using descriptive statistics (for example, n, mean, median, standard deviation, minimum, and maximum) by treatment arm and time points. A mixed effects model, repeated measures model will be applied to compare between treatment arms, which may be adjusted for other covariates. 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, ≥50% of the

questions were answered). Separate similar analyses will be conducted using the average of the BPI-sf/worst pain assessments associated with each cycle.

12.2.11.2. Pain Assessment

Pain analysis will be based on all randomized patients with at least 1 baseline BPI "worst pain" and one BPI "worst pain" score on Cycle 2 Day 1 or later.

The mBPI-sf will be administered at baseline prior to study drug dosing and the Cycle 1, Day 1 score will be treated as a baseline observation and the Day 1 score of each subsequent cycle will be attributed to the previous cycle. The mBPI-sf will be administered at treatment discontinuation and grouped with observations from the previous cycle.

Time to worsening in pain will be described using the method of Kaplan and Meier and will be made between 2 arms by a log-rank test. "Worsening" will be defined as either a "worst pain" increase of $\geq$2 points postbaseline or an analgesic drug class increase of $\geq$1 level. Worsening rate at Years 1, 2, and 3 will be estimated and compared between the 2 arms. Number of events due to each criterion will be described.

12.2.11.3. Health-Related Quality of Life

EORTC QLQ-C30 instrument data will be scored as described by Aaronson and colleagues (Aaronson et al. 1993). If not already addressed in the EORTC scoring manual (Fayers et al. 2001), descriptive statistics for each EORTC QLQ-C30 item will be calculated. Frequency distributions and measures of central tendency and variability (for example, n, mean, median, standard deviations, minimum, and maximum) will be calculated for each dimension and the total score, and compared between arms.

EORTC QLQ-BR23 data will be scored as described by the EORTC scoring manual (Fayers et al. 2001).

12.2.11.4. Utilization

Utilization data will be summarized descriptively by category across arms (for example, analgesic use, bisphosphonate use, transfusions, radiation, surgery, and hospitalization days), including a frequency table with tabular statistics. For categorical variables, frequency and the corresponding percentage will be derived and measures of central tendency and variability (for example, n, mean, median, standard deviations, minimum, and maximum) will be calculated for continuous variables. Tests for differences in proportion between treatment groups and between response groups will be performed. Exploratory analyses may be performed to investigate associations between the utilization data and the clinical endpoints.

12.2.11.5. Health State Utility

The EQ-5D 5L data will be scored as described in an article that is under review for publication (van Hout et al. 2012). The index score is calculated from a set of item weights to derive a score of 0 to 1, with 1 representing the best health status. Geographic-specific weights will be used as appropriate and when available. The VAS is scored from 0 (*worst imaginable health state*) through 100 (*best imaginable health state*) to represent the patient's self-report for each day. EQ-5D 5L responses for each item will be summarized by frequency and corresponding

percentages. Descriptive statistics for the index and VAS will be calculated, including (n, mean, median, standard deviations, minimum, and maximum) Psychometric analyses, including calculation of reliability coefficients (Cronbach's alpha), will also be performed. The index scores and VAS may be analyzed using a mixed effects analysis of variance model. Of interest is a significant time-by-group interaction for each of the items, addressing whether treatment group profiles are different over time (from randomization through the last assessment following discontinuation).

12.2.11.6. Time to First Skeletal-Related Event (TT1SRE)

Time from randomization to documentation of the first occurrence of any SRE will be evaluated. Patients not known to have had an SRE at the time of the analysis will be censored at the date of their last complete documented assessment for SRE. A stratified log-rank test will be used to evaluate the difference of time to first SRE between treatments. Stratification factors will include whether a patient had at least 1 SRE prior to randomization, and the presence of bone lesions, as well as those factors used to stratify treatment randomization.

12.2.11.7. Time to Worsening ECOG Performance Status

Time from randomization to documentation of the first occurrence of any PS of ≥2 will be evaluated. Log-rank test will be used to evaluate the difference of time to worsening in ECOG between treatments.

12.2.11.8. Exploratory Analyses

Joint modeling may be explored to characterize the relationship between features of the longitudinal PRO trajectories (individual items or composite scores) and the event times.

Time from randomization to earliest development of new bone metastases may be analyzed and compared between arms.

Proportion of patients who experience a "worst pain" increase of ≥2 points at any post-baseline visit (on or after Day 1 Cycle 2) will be compared between treatment arms. Changes in analgesic and bone agent use will be collected and summarized by arms.

12.2.12. Safety Analyses

All safety summaries and analyses will be based upon the Safety Population as defined in Section 12.2.1.

Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. The number of patients with any dose adjustment will be presented for entire treatment period as well as for each cycle. The number of patients with dose reductions, dose delays, or dose omissions will also be summarized, as will the reasons for dose adjustments.

AEs will be reported using a unified CTCAE/MedDRA reporting process:

- The CTCAE v4.0 term reported by the investigator will be mapped to the MedDRA Preferred Term (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.

Preexisting conditions are defined as adverse events 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. Comparisons of preexisting conditions to on-treatment events at the LLT level will be used in the treatment-emergent computation.

The following summaries will be produced by PT within SOC: preexisting conditions, SAEs, TEAEs, drug-related TEAEs, and procedure-related TEAEs.

The following summaries will be produced by PT within SOC and maximum CTCAE grade: laboratory-based TEAEs, nonlaboratory-based TEAEs, drug-related laboratory-based TEAEs, and drug-related nonlaboratory-based TEAEs.

Reasons for death will be summarized separately for on-therapy and within 30 days of treatment discontinuation.

Hospitalizations and transfusions during the study treatment period or during the 30-day short-term follow-up period will be summarized by treatment group.

12.2.13. Subgroup Analyses

Subgroup analyses of PFS and OS will be performed for each of following potential prognostic subgroup variables:

- All baseline stratification factors
- Measurable disease at baseline (yes versus no)
- Number of organs involved (1 versus 2 vs. 3+)
- Age (<65 years versus ≥65 years)
- Region (North America, Europe, Asia, and Other)
- Race (Caucasian, Asian, and Other)
- PgR status (positive versus negative)
- Baseline ECOG PS (0 versus 1)

If a level of a factor consists of fewer than 5% of randomized patients, analysis within that level may be omitted.

Analyses will be done within subgroup and, separately, across subgroups with a test of interactions of subgroups with treatment performed.

Other subgroup analyses may be performed as deemed appropriate. If any safety analyses described in Section 12.2.12 identify important imbalances between arms, subgroup analyses of these endpoints may be performed.

12.2.14. Interim Analyses

12.2.14.1. Safety Interim Analyses

The DMC is responsible for providing external oversight of patient safety in Study JPBL independently of the Lilly study team and Lilly GPS.

During the study, safety interim analyses will be performed every 3 months. The first safety interim analysis will be triggered by the 90th patient enrolling, with the data cutoff for this analysis occurring 1 month after the trigger. The safety interim analyses will be conducted to evaluate the overall safety profile of abemaciclib when given in combination with fulvestrant. At the recommendation of the DMC, the frequency of safety interim analyses may be modified.

At each interim analysis, the DMC may recommend the trial continue without modifications, continue with specific modifications, or be stopped for safety concerns. There will be no prespecified rules for stopping the trial due to safety concerns. The DMC members will review unblinded safety data at each interim analysis. If a significant safety signal is identified, the DMC may recommend a protocol amendment, termination of enrollment, and/or termination of study treatment. The recommendations of the DMC will be communicated to the Lilly SMD and, if necessary, an IRC.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the treatment group level, members of the DMC can conduct additional analyses of the safety data. Additionally, unblinding of a limited number of Lilly representatives external to the study team may be required for evaluation of selected SAEs for determination of regulatory reporting.

12.2.14.2. Efficacy Interim Analyses

One efficacy interim analysis of PFS and 3 interim analyses of OS (1 corresponding to the interim PFS analysis and 1 corresponding to the primary PFS analysis) are planned, as described in Sections 12.2.6 and 12.2.7. The interim PFS analysis will be conducted to provide early efficacy information and could potentially result in early communication with regulatory agencies. If the analysis of PFS is significant using the cutoff described in Section 12.2.6, the DMC will be instructed to engage the SMD, who may subsequently convene an IRC to propose actions based upon the DMC's recommendation. OS will be analyzed as described is Section 12.2.7. Results of OS analyses will not be communicated until a significant result is observed or the primary PFS analysis is performed.

The sponsor has no intent to stop the study based on interim analysis of efficacy, and all patients will continue follow-up for PFS and OS until study close. Patients randomized to the control group will not be permitted to cross over to the experimental group in case early efficacy is observed during interim review, as this will confound the assessment of OS.

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

Unblinding details are specified in the unblinding plan section of the SAP.

12.2.14.3. Pharmacokinetic/Pharmacodynamic Interim Analyses

A limited number of preidentified individuals independent of the study team may receive access to unblinded data, as specified in the unblinding plan, prior to the interim or final database lock, in order to initiate the final population PK/pharmacodynamic model development processes for interim or final analyses. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s).

The study site's ERB(s) should be provided with the following:

- the current IB or package labeling and updates during the course of the study
- ICF
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- the ICH GCP Guideline (E6)
- applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of Lilly will be assigned to a third-party organization.

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Site-specific contact information may be provided in a separate document.

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The clinical study report (CSR) coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Lilly will select an investigator to serve as the CSR coordinating investigator.

The Lilly responsible medical officer and statistician will sign/approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol JPBL Study Schedule

Study Schedule, Protocol I3Y-MC-JPBL

Perform procedure as indicated.

			Baseline		Patients on Study Treatment				Postdiscontinuation Follow-Up	
		Cycle	BL		1		2 – 3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]
		Visit	0		1		2 – 3	4 and Beyond (if Applicable)	801	802 - 8XX
		Approximate Duration (days)	28		28		28	28	30	Variable
		Relative day within a cycle	≤28	≤14	1	15±3	1[p]	1[p]		
Procedure Category	**Procedure**	**Protocol Reference**								
Study Entry /Enrollment	Informed Consent Form signed[q]	Section 8.1	X[q]							
	Inclusion/Exclusion evaluation	Section 7		X						
Medical History	Medical History			X						
	Historical illnesses	Section 12.2.3		X						
	Habits assessment	Section 12.2.3		X						
Physical Examination	Height	Section 12.2.3		X						
	Weight	Section 12.2.3		X	X	X	X	X	X	
	Vital Signs (Temp, BP, HR, RR)	Section 12.2.3		X	X	X	X	X	X	
	ECOG performance status	Section 7.1 Attachment 4		X	X	X	X	X	X	
Tumor Assessment	Tumor measurement (palpable or visible)[c]	Section 10.1.1	X[c]				X[c]	X[c]	X[c]	X[c]
	Radiologic imaging according to RECIST[b]	Section 10.1.1 Attachment 5	X[b]				X[b]	X[b]	X[b]	X[b]
	Bone Scintigraphy[i]	Section 10.1.1 Attachment 5	X[i]					X[i]	X[i]	X[i]
	X-ray or CT scan with bone windows or MRI[j]	Section 10.1.1 Attachment 5	X[j]				X[j]	X[j]	X[j]	X[j]

			Baseline		Patients on Study Treatment				Postdiscontinuation Follow-Up	
		Cycle	BL		1		2 – 3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]
		Visit	0		1		2 – 3	4 and Beyond (if Applicable)	801	802 - 8XX
		Approximate Duration (days)	28		28		28	28	30	Variable
		Relative day within a cycle	≤28	≤14	1	15±3	1[p]	1[p]		
Procedure Category	**Procedure**	**Protocol Reference**								
Survival Information[d]		Section 10.1							X[d]	X[d]
Adverse Event Collection/CTCAE Grading[f]		Section 10.3		X[f]	X[f]		X[f]	X[f]	X[f]	X[f]
Concomitant Medications (with analgesics)		Section 9.6		X	X		X	X	X	
Lab/ Diagnostic Tests	Central hematology	Attachment 2		X	X	X	X	X	X	
	Central serum chemistry	Attachment 2		X	X	X	X	X	X	
	Local FSH and estradiol levels[n]	Attachment 2		X[n]						
	Local serum pregnancy test[o]	Attachment 2		X[o]						
	Central pharmacokinetic (PK) sampling[m]	Attachment 7			X[m]	X[m]	X[m]			
	Pharmacogenetic blood sample	Section 10.4.2.2			X					
	Biomarker plasma sample	Section 10.4.2.3			X					
	Local ECG[e]	Section 10.3.2.1		X[e]	X[e]	X[e]		X[e]	X[e]	
	Archived Tumor Sample[h]	Section 10.4.2.1			X[h]					

			Baseline		Patients on Study Treatment				Postdiscontinuation Follow-Up	
		Cycle	BL		1		2 – 3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]
		Visit	0		1		2 – 3	4 and Beyond (if Applicable)	801	802 - 8XX
		Approximate Duration (days)	28		28		28	28	30	Variable
		Relative day within a cycle	≤28	≤14	1	15±3	1[p]	1[p]		
Procedure Category	**Procedure**	**Protocol Reference**								
Study Drug	Fulvestrant Therapy [g]	Section 9.1			Days 1 and 15 of Cycle 1, then Day 1 of Cycle 2 and beyond[g]					
	Abemaciclib or Placebo Therapy[g]	Section 9.1			Q12H on Days 1 through 28 of every cycle[g]					
Health Outcomes	BPI, EORTC QLQ-C30, EORTC BR23, EQ-5D 5L[k]	Section 12.2.11		X[k]			X[k]	X[k]	X[k]	
	Skeletal-Related Events assessment[l]	Section 12.2.11		X[l]			X[l]	X[l]	X[l]	X[l]
	Hospitalization	Section 12.2.11.4		X			X	X	X	
	Transfusion	Section 12.2.11.4		X			X	X	X	

Abbreviations: BL = baseline; Temp = Temperature; BP = Blood Pressure; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; GnRH = gonadotropin-releasing hormone; HR = heart rate; IV = intravenous; PK = pharmacokinetics; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; Q12H = every 12 hours; SAEs = serious adverse events; FSH = follicular stimulating hormone.

a Short-term follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days; the associated study procedures are performed once at the end of this period. Long-term follow-up begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion; the associated study procedures are performed approximately every 12 weeks (± 14 days) for the duration of this period.

Study Schedule, Protocol I3Y-MC-JPBL (continued)

b For patients with inoperable locally advanced breast cancer, MRI scan of the breast is performed locally at baseline (Day -28 to Day -1), between Day 1 and Day 7 of every second cycle beginning with Cycle 3 and continuing through Cycle 13, between Day 1 and Day 7 of every third cycle after Cycle 13, and within 14 days of clinical progression. For all patients, CT or MRI scan of the chest, abdomen, and pelvis is performed locally at baseline (Day -28 to Day -1), between Day 1 and Day 7 of every second cycle beginning with Cycle 3 and continuing through Cycle 13, between Day 1 and Day 7 of every third cycle after Cycle 13, and within 14 days of clinical progression. It is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast whenever possible. If this is not feasible due to hypersensitivity or other conditions, then gadolinium-enhanced MRI is preferred. For patients with known serious allergic reactions to CT contrast material, a CT of the chest without contrast and gadolinium-enhanced MRI of the abdomen/pelvis are encouraged. For patients who discontinue study treatment without objectively measured progressive disease (PD), continue to evaluate tumor response approximately every 8 weeks for the first 12 months following randomization and thereafter approximately every 12 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression or until study completion. After the patient has objective disease progression, radiologic tests are no longer required and the patient will continue with post-discontinuation follow-up until the patient's death or overall study completion.

c Visible tumor (such as skin lesions) should be documented by photography and each photographic image of the tumor should include a ruler. For patients who discontinue study treatment without objectively measured progressive disease (PD), continue to evaluate tumor response approximately every 8 weeks for the first 12 months following randomization and thereafter approximately every 12 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression or until study completion. After the patient has objective disease progression, tumor assessments are no longer required and the patient will continue with post-discontinuation follow-up until the patient's death or overall study completion.

d Survival information is collected at baseline and during both study treatment and postdiscontinuation follow-up. During Long-Term Follow-Up, survival information is collected approximately every 12 weeks for the duration of this period. Although preferable to collect during a clinic visit, survival information may be collected by contacting the patient or family directly (for example, via telephone). Long-Term Follow-up data collection may include anticancer therapies.

e A local ECG (no replicates required) should be obtained at baseline (Day -14 to Day -1), 2 to 4 hours after the LY dose on Cycle 1 Day 1, upon arrival at site but prior to fulvestrant dose on Cycle 1 Day 15, 2 to 4 hours after the LY dose on Cycle 4 Day 1, and at the short-term follow-up visit.

f Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System. During Long-Term Follow-Up, only SAEs that are related to study drugs or protocol procedures will be collected. All adverse events possibly related to study drugs or protocol procedures should be followed until they resolve, are no longer considered to be possibly related, become stable or return to baseline, the patient starts a new therapy, the patient expires, or the patient becomes lost to follow-up. The frequency of evaluation is determined according to the judgment of the investigator.

g Blinded study drug should be administered orally Q12H on Days 1 through 28 of each cycle; patients should not consume food beginning 1 hour before and ending 1 hour after taking blinded study drug. Fulvestrant 500 mg should be administered intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock; however, for patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection.

h Formalin-fixed paraffin-embedded tumor tissue (either block or 15-20 unstained slides) should be requested at the time of randomization. However, if this sample is not available for a patient, it will not constitute a protocol deviation

Study Schedule, Protocol I3Y-MC-JPBL (concluded)

i Bone scintigraphy is performed locally at baseline (Day -28 to Day -1) for all patients. If available, prior bone scintigraphy (obtained as part of routine clinical care) within 45 days before Day 1 of Cycle 1 is also acceptable. Bone scintigraphy should be repeated for all patients between Day 1 and Day 7 of every sixth cycle beginning with Cycle 7, when complete response is identified in target disease, or when progression in bone is suspected. Importantly, RECIST v1.1 emphasizes that bone scintigraphy is not adequate to measure bone lesions; however, bone scintigraphy can be used to confirm the presence or disappearance of bone lesions. For patients who discontinue study treatment without objectively measured progressive disease (PD), continue to evaluate tumor response approximately every 6 months until the patient has objective disease progression or until study completion. After the patient has objective disease progression, bone scintigraphy is no longer required and the patient will continue with post-discontinuation follow-up until the patient's death or overall study completion.

j One or more of these studies [X-ray, CT scan with bone windows, or MRI] is performed locally at baseline (Day -28 to Day -1), between Day 1 and Day 7 of every second cycle beginning with Cycle 3 and continuing through Cycle 13, between Day 1 and Day 7 of every third cycle after Cycle 13, and within 14 days of clinical progression only for patients with bone lesions identified by bone scintigraphy at baseline. For patients with new lesions identified by post-baseline bone scintigraphy, targeted assessment by X-ray, CT scan with bone windows, or MRI will be performed to confirm findings. For patients who discontinue study treatment without objectively measured progressive disease (PD), continue to evaluate tumor response approximately every 8 weeks for the first 12 months following randomization and thereafter approximately every 12 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression or until study completion. After the patient has objective disease progression, radiologic tests are no longer required and the patient will continue with post-discontinuation follow-up until the patient's death or overall study completion.

k mBPI-sf, EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D 5L should be administered at baseline (Day -14 to Day -1), Cycle 2 Day 1, and then on Day 1 of every second cycle beginning with Cycle 3 and continuing through Cycle 13, on Day 1 of every third cycle after Cycle 13, and at Short-Term Follow-Up. Patients should complete these assessments before extensive interaction with site staff.

l Skeletal-Related Events include pathological fracture, spinal cord compression, radiation to bone, and surgery to bone.

m See Pharmacokinetic Sampling Schedule (Attachment 7).

n FSH and estradiol levels are required only for women age <60 years and amenorrheic for at least 12 months.

o A serum pregnancy test is required only for patients receiving ovarian suppression with a GnRH agonist.

p For Cycle 2 and beyond, the start of a cycle may be delayed up to 7 days for logistical reasons and up to 14 days to allow sufficient time for recovery from toxicity possibly related to a study drug. Refer to Section 9.4.1.1.2.

q Informed Consent Form is signed within 28 days prior to randomization of study drug and prior to performance of any protocol-specific tests/procedures.

Study Schedule for the extension period only, Protocol I3Y-MC-JPBL

Perform procedure as indicated.

			Patients on Study Treatment		Extension Period Follow-Up
		Cycle	X-Y		Follow-Up[a]
		Visit	501-5XX		901
		Duration (days)	28		30
		Relative day within a cycle	1	15	
Procedure Category	**Procedure**	**Protocol Reference**			
Adverse Events Collection/CTCAE Grading[b]		Section 10.3	X		X
Study Drug	Fulvestrant Therapy[c]	Section 8.1.2	Days 1 and 15 of Cycle 1, then Day 1 of Cycle 2 and beyond[c]		
	Abemaciclib Therapy[c]	Section 8.1.2	Daily Q12H[c]		

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; PK = pharmacokinetics; Q12H = every 12 hours; SAEs = serious adverse events.

a The extension period begins after study completion and ends at the end of trial.

b Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system.

c Abemaciclib should be administered Q12H on Days 1 through 28 of each cycle. Patients should not consume food beginning 1 hour before and ending hour after taking study drug.
Fulvestrant 500 mg should be administered intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock; however, for patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection.

Attachment 2. Protocol JPBL Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]:	**Clinical Chemistry**[a]:
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
	Chloride
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Total bilirubin
Mean cell hemoglobin concentration (MCHC)	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils (segmented + bands)	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Calcium
Platelets	Total Protein
	Albumin
	Serum Pregnancy Test[b,c] (only for patients receiving ovarian suppression with a GnRH agonist)
	FSH level[b,c]
	Estradiol level[b,c]

Abbreviations: FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; RBC = red blood cells; WBC = white blood cells.

a Lilly-designated laboratory.

b Local- or investigator-designated laboratory.

c To be performed at baseline only in order to establish eligibility. FSH and estradiol levels are required only for women age <60 years and amenorrheic for at least 12 months.

Attachment 3. Protocol JPBL Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented and bands	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 4. Protocol JPBL ECOG Performance Status

ECOG Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead.

Source: Oken et al. 1982.

Attachment 5. Protocol JPBL RECIST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the case record form (CRF) in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

Pet Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

Partial Response (PR): At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10mm short axis).

Non-CR/ non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The Best Overall Response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 1. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PR = partial response; SD = stable disease.; PD = progressive disease; NE = inevaluable.

Table 2 is to be used when patients have *nonmeasurable* disease only.

Table 2. Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease; NE = inevaluable.

[a] non-CR/non-PD is preferred over SD for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6-8 weeks is reasonable. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from randomization.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Independent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Attachment 6. Protocol JPBL Sampling Summary

This table summarizes the purpose for sampling, sample types, maximum volume per sample, maximum number of samples, and maximum total volume during the study. The summary below provides estimates. More samples could be required in the case of retests, additional health monitoring (if needed), or for patients continuing treatment beyond the protocol-specified number of cycles in the study. Fewer samples may actually be taken (for example, patients who discontinue from the study).

Protocol I3Y-MC-JPBL Sampling Summary[a]

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Screening/Study qualification (Hematology and Clinical Chemistry)	Blood	7 mL	1	7 mL
Safety/Health monitoring (Hematology and Clinical Chemistry)	Blood	7 mL	11	77 mL
Pharmacokinetic sample	Blood	4 mL	6	24 mL
Pharmacogenetic blood sample	Blood	10 mL	1	10 mL
Biomarker plasma sample	Blood	6 mL	1	6 mL
Total blood volume	Blood			124 mL
Hepatic monitoring[b]	Blood	3 - 30 mL	-	-

a Covers Cycles 1 through 9.

b Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with the designated medical monitor.

Attachment 7. Protocol JPBL Pharmacokinetic Sampling Schedule

The schedule for PK sampling is summarized in the table below. The date and exact time of collection for each venous blood sample should be documented on the laboratory requisition.

Pharmacokinetic Sampling Schedule

PK Sample Number	Cycle (C) and Day (D)	Dosing of Abemaciclib or Placebo (Blinded Study Drug)	Dosing of Fulvestrant	Sampling Time for PK from Blood[a]
1	C1D1	X	X	2 to 4 hrs after fulvestrant and blinded study drug dose
2	C1D15	X[b]	X	Upon arrival at site but prior to fulvestrant dose (that is, at least 4 hrs after taking blinded study drug dose at home)
3	C1D15			3 ± 0.5 hrs after PK Sample Number 2 (that is, at least 7 ± 0.5 hrs after taking blinded study drug dose at home)
4	C2D1	X	X	Prior to fulvestrant and blinded study drug dose
5	C2D1			3 ± 0.5 hrs after blinded study drug dose
6	C3D1	X	X	Prior to fulvestrant and blinded study drug dose

Abbreviations: hr = hour; PK = pharmacokinetic.

a Samples of approximately 4 mL of whole blood will be drawn. After obtaining plasma, site personnel will aliquot samples into 2 approximately equal portions, one for measurement of LY2835219 and its metabolites concentrations and the other for measurement of fulvestrant concentrations. Only samples No. 1, 2, 4, and 6 will be used for measurement of fulvestrant.

b On Cycle 1 Day 15 only, patient should take blinded study drug dose at home at least 4 hours before arrival at site. The time of blinded study drug dose intake must be recorded that day.

Attachment 8. Protocol JPBL Inducers and Strong Inhibitors of CYP3A4

The information in this attachment is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Inducers of CYP3A4
Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St. John's wort
Strong inhibitors of CYP3A4
All HIV protease inhibitors
Clarithromycin
Itraconazole
Ketoconazole
Nefazodone

[a] Important note: A patient who develops brain metastases may receive acute or chronic therapy with dexamethasone if clinically indicated. All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated.

Attachment 9. Protocol JPBL CTCAE 4.03 Diarrhea Definition

Diarrhea will be evaluated in this study using the criteria proposed by Common Terminology Criteria for Adverse Events (CTCAE) v4.0 revised: CTCAE 4.03-June 14, 2010: Gastrointestinal disorders.

Gastrointestinal Disorders					
Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase <= 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: a disorder characterized by frequent and watery bowel movements					

Abbreviation: ADL = Activities of Daily Living.

Attachment 10. Protocol JPBL Amendment(a) Summary MONARCH 2: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer

Study I3Y-MC-JPBL A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version.

The overall changes made to this protocol are as follows:

- Inclusion of clinical trial name, MONARCH 2, in study trial title, Synopsis, and Sections 1, 3, and 5
- Replacement of LY2835219 with abemaciclib throughout document
- Replacement of LY2835219/placebo with blinded study drug throughout document
- Section 5.1 brief rationale for amendment
- Section 5.2 dose rationale to reduce blinded study drug to 150 mg
- Sections 9.4.1.1.4, 9.4.1.1.4.1, and 9.6.5 and Attachment 9 management for diarrhea has been modified

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of <u>underscore</u>.

1. Protocol I3Y-MC-JPBL

MONARCH 2: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without ~~LY2835219~~Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer

LY2835219 (Abemaciclib)

This study is a global, multicenter, double-blind, placebo-controlled, Phase 3 trial for women with hormone receptor positive, HER2 negative locally advanced or metastatic breast cancer randomized to receive fulvestrant with or without ~~LY2835219~~abemaciclib.

Protocol ~~Electronically Signed and~~ Approved by Lilly: 01 April 2014
Amendment (a) Electronically Signed and Approved by Lilly on date provided below.

2. Synopsis

Study Rationale

~~LY2835219~~Abemaciclib is an oral, selective, and potent small molecule cyclin-dependent kinases (CDKs) 4 and 6 (CDK4/6) dual inhibitor with antitumor activity within multiple preclinical pharmacology models and an acceptable toxicity profile in nonclinical species. ~~LY2835219~~Abemaciclib mesylate has been shown to significantly inhibit tumor growth in multiple murine xenograft models for human cancer. Published studies that evaluated in vitro growth inhibition with other CDK4/6 inhibitors across a diverse panel of 47 breast cell lines showed greater sensitivity to CDK4/6 inhibition in estrogen receptor positive (ER+) lines. Specifically, studies with ~~LY2835219~~abemaciclib indicate differential sensitivity to CDK4/6 inhibition based on histological and genetic characteristics. Growth inhibition in vitro across a diverse panel of 46 breast cancer cell lines, representing the known molecular subgroups of breast cancer, indicates that sensitivity to CDK4/6 inhibition is greater in ER+ breast cancers with luminal histology.

Importantly, ~~LY2835219~~abemaciclib has demonstrated evidence of clinical activity in a tumor-specific cohort of women with metastatic breast cancer (mBC). In Study I3Y-MC-JPBA, 47 patients with a median of 7 prior systemic regimens received therapy with ~~LY2835219~~abemaciclib. Among the 36 patients with hormone receptor positive (HR+) mBC, the median progression-free survival (PFS) was ~~9.1~~8.8 months~~(with 18 patients still on LY2835219abemaciclib therapy)~~and there were ~~9~~ 12 confirmed partial responses (PR) for an objective response rate of ~~25~~33.3%. In the same study, the combination of ~~LY2835219~~abemaciclib plus fulvestrant was also evaluated and demonstrated an acceptable safety profile in 19 women with HR+ mBC. In addition, 4 confirmed partial responses were observed in these 19 patients. These results support further investigation of ~~LY2835219~~abemaciclib in combination with fulvestrant for women with HR+ locally advanced or metastatic breast cancer.

Study I3Y-MC-JPBL is a randomized, double-blind, placebo-controlled Phase 3 study of fulvestrant with or without ~~LY2835219~~abemaciclib for women with HR+, human epidermal growth factor receptor 2 negative (HER2-) locally advanced (not amenable to curative treatment by surgery) or metastatic breast cancer.

Clinical Protocol Synopsis: Study I3Y-MC-JPBL

Name of Investigational Product: Abemaciclib (LY2835219)
Title of Study: MONARCH 2: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without ~~LY2835219~~Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer
Objectives: The primary objective of Study I3Y-MC-JPBL (JPBL) is to compare ~~LY2835219~~abemaciclib plus fulvestrant versus placebo plus fulvestrant with respect to PFS for women with HR+, HER2- locally advanced or metastatic breast cancer. The secondary objectives of the study are to compare ~~LY2835219~~abemaciclib plus fulvestrant versus placebo plus fulvestrant with respect to each of the following: • pain and symptom burden using the Brief Pain Inventory (BPI), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the EORTC QLQ-BR23 (breast) questionnaires, and health status scores from the EuroQol 5-Dimension 5 Level (EQ-5D 5L) • pharmacokinetics (PK) of ~~LY2835219~~abemaciclib, its metabolites, and fulvestrant • time to worsening of Eastern Cooperative Oncology Group (ECOG) performance status of ≥2 • time to first skeletal-related event (SRE; defined as either pathological fracture, spinal cord compression, radiation to the bone, or surgery to the bone)
Diagnosis and Main Criteria for Inclusion and Exclusions: Patients are eligible to be included in the study if they meet following criteria: 1) have a diagnosis of HR+, HER2- breast cancer; 2) have inoperable locally advanced or metastatic disease and relapsed with radiologic evidence of progression after prior endocrine therapy or have not received prior endocrine therapy; 3) have postmenopausal status due to either surgical/natural menopause or ovarian suppression with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin; 4) have a negative serum pregnancy test at baseline (within 14 days prior to randomization) and agree to use medically approved precautions to prevent pregnancy during the study and for 12 weeks following the last dose of ~~LY2835219~~abemaciclib if postmenopausal status is due to ovarian suppression with a GnRH agonist; 5) have either measurable disease or nonmeasurable bone only disease; 6) are female and ≥18 years of age; 7) have given written informed consent prior to any study-specific procedures; 8) have adequate organ function; 9) have a performance status ≤1 on the ECOG scale; 10) have discontinued previous therapies for cancer, for at least 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents prior to receiving study drug, and recovered from the acute effects of therapy;11) are willing to participate for the duration of the study and to follow study procedures; and 12) are able to swallow capsules. Patients will be excluded from the study if they meet any of the following criteria: 13) are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study; 14) have visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis; 15) have a history of central nervous system metastasis; 16) have received prior treatment with chemotherapy (except for neoadjuvant/ adjuvant chemotherapy), fulvestrant, everolimus, or any CDK4/6 inhibitor; 17) have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days prior to randomization of study drug for a nonmyelosuppressive or myelosuppressive agent, respectively; 18) have received recent (within 28 days prior to randomization) yellow fever vaccination; 19) have had major surgery within 14 days prior to randomization~~of the initial dose of study drug~~; 20) have a personal history of any of the following conditions: presyncope or syncope of either unexplained or cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest; 21) have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study; 22) have inflammatory breast cancer or a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years; 23) have received an autologous or allogeneic stem-cell transplant; 24) have active bacterial or fungal infection, or detectable viral infection; or 25) are pregnant or breastfeeding.

Test Product, Dosage, and Mode of Administration:
~~LY2835219~~Abemaciclib will be supplied as capsules administered orally, ~~200~~150 mg every 12 hours (Q12H) on Days 1 to 28 of a 28-day cycle, plus fulvestrant will be administered 500 mg intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock, on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond.

Reference Therapy, Dose, and Mode of Administration: Placebo will be supplied as capsules administered orally Q12H~~every 12 hours~~ on Days 1 to 28 of a 28-day cycle plus fulvestrant will be administered 500 mg intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock, on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond.

Criteria for Evaluation:

Safety:

- Adverse events using NCI CTCAE Version 4.0~~3~~

Health Outcomes:

- BPI: proportion of patients with "worst pain" increase of 2 points or more at any time on-therapy, compared to baseline
- EORTC QLQ-C30 and EORTC QLQ-BR23: Describe target tumor symptom changes
- EQ-5D 5L: Describe health status changes
- ~~Changes in utilization between arms (e.g. analgesic, hospitalization, transfusion)~~

Pharmacokinetics:

- Population PK parameters for ~~LY2835219~~abemaciclib and fulvestrant
- Plasma concentration levels of fulvestrant during Cycle 1/Cycle 2

Exploratory

- Potential biomarkers related to the Rb pathway and/or the pathogenesis of breast cancer.
- Time course of change in tumor size

Statistical Methods:

Statistical: The primary objective of this study is to compare ~~LY2835219~~abemaciclib plus fulvestrant versus placebo plus fulvestrant in terms of PFS for women with HR+, HER2- locally advanced or metastatic breast cancer. An important secondary objective of this study is to compare the 2 arms with respect to OS.

A 2-look group sequential design on the primary endpoint of PFS will be utilized, with interim and primary PFS analyses occurring at approximately 270 PFS events and 385 PFS events, respectively. The Lan-Demets method with an O'Brien-Fleming like spending function will be used to maintain the cumulative 1-sided Type I error rate of .025. Assuming a hazard ratio (HR) of 0.703, this design yields at 90% statistical power to detect superiority of the ~~LY2835219~~abemaciclib plus fulvestrant arm over placebo plus fulvestrant arm with the use of a 1-sided log-rank test and a cumulative type I error rate of 0.025.

OS is an important secondary endpoint for this study. OS will be tested only if the test of PFS is significant. A 4-look approach to testing OS with a cumulative 1-sided type I error rate of .025 will be utilized to allow for analyses of OS at the interim PFS analysis, the primary PFS analysis, 289 OS events, and 385 OS events (final OS analysis).

Efficacy:

The PFS and OS analyses to test the superiority of ~~LY2835219~~abemaciclib to placebo in improving PFS and OS time will use the log-rank test stratified by stratification variables. Additional analyses will be performed using the Kaplan-Meier method to estimate the PFS and OS curves and rates, and the Cox proportional hazard model will be used to estimate the PFS and OS HRs and corresponding 95% confidence interval.

Pharmacokinetics:

PK parameters for ~~LY2835219~~abemaciclib in plasma (clearance, exposure, volume of distribution, and half-lives) and inter-individual PK variability will be computed using nonlinear mixed effect modeling implemented in NONMEM. If warranted by the data, PK parameters for fulvestrant in plasma and inter-individual variability

estimates will also be computed using nonlinear mixed effect modeling implemented in NONMEM.

Pharmacodynamics:
Pharmacodynamic data (such as neutrophil, lymphocytes, or platelets counts in blood) may be analyzed by means of NONMEM and connected to the population PK model for ~~LY2835219~~abemaciclib and/or fulvestrant in a PK/pharmacodynamic model.

Tailoring biomarkers:
Summary statistics will include means, medians, corresponding standard errors, quartiles, and ranges. Biomarkers with discrete measures, such as genotype locus, will be summarized in frequency tables. Correlative analyses may be performed to investigate associations between biomarkers and clinical endpoints.

MONARCH 2: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without ~~LY2835219~~Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer

5. Introduction

~~LY2835219~~Abemaciclib is a potent and selective small molecule inhibitor of CDK4/6. In the Phase 1 Study I3Y-MC-JPBA (JPBA), ~~LY2835219~~abemaciclib has shown acceptable safety across five tumor-specific cohorts, with the most common treatment-emergent adverse events (TEAEs) possibly related to study drug including diarrhea, nausea, fatigue, vomiting, and neutropenia. Importantly, ~~LY2835219~~abemaciclib has demonstrated evidence of clinical activity in a tumor-specific cohort of women mBC. In Study I3Y-MC-JPBA, 47 patients with a median of 7 prior systemic regimens received therapy with ~~LY2835219~~abemaciclib. Among the 36 patients with HR+ mBC, the median progression-free survival (PFS) was ~~9.1~~8.8 months ~~(with 18 patients still on LY2835219abemaciclib therapy)~~ and there were ~~9~~ 12 confirmed partial responses (PR) for an objective response rate of ~~25~~33.3%. In the same study, the combination of ~~LY2835219~~abemaciclib plus fulvestrant was also evaluated and demonstrated an acceptable safety profile in 19 women with HR+ mBC. In addition, ~~four~~4 confirmed partial responses were observed in these 19 patients. These results support further investigation of ~~LY2835219~~abemaciclib in combination with fulvestrant for women with HR+ locally advanced or metastatic breast cancer.

Study I3Y-MC-JPBL is a randomized, double-blind, placebo-controlled Phase 3 study of fulvestrant with or without ~~LY2835219~~abemaciclib for women with HR+, human epidermal growth factor receptor 2 negative (HER2-) locally advanced (not amenable to curative treatment by surgery) or metastatic breast cancer.

More information about the known and expected benefits and risks of ~~LY2835219~~abemaciclib may be found in the Investigator's Brochure (IB). Information on adverse events (AEs) expected to be related to the study drug may be found in Section 7 (Development Core Safety Information) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

5.1. Rationale for Amendment (a)

This protocol was amended so that the initial dose of abemaciclib when administered in combination with fulvestrant could be lowered from 200 mg every 12 hours (Q12H) to 150 mg Q12H.

Additionally, existing patients who have already started on 200 mg of blinded study drug will be dose reduced to 150 mg Q12H.

Further modifications were performed for clarity: 1) blinded study drug in relevant places defined; 2) supportive management for diarrhea modified. Minor typographical and formatting edits were made throughout the document for clarity and consistency.

5.2. Dose Rationale

The rationale for reducing and selecting the starting dose was based on the preliminary blinded safety review of Study JPBL and updated safety and pharmacokinetic/pharmacodynamic (PK/PD) data from patients treated with endocrine therapies in combination with abemaciclib in advanced or metastatic breast cancer enrolled in Studies JPBA and JPBH.

Pharmacokinetic data obtained in Study JPBA for abemaciclib from a total of 124 patients dosed repeatedly with abemaciclib at 150 and 200 mg Q12H indicate that the range of steady-state exposures achieved with 150 mg Q12H is comparable to 200 mg Q12H. In addition, in Study JPBA the steady-state exposures achieved with a 50-mg unit dose, which is the lowest possible allowed dose in Study JPBL in the case of dose reduction when needed for AEs, are within the low end of the range of exposures achieved by the 150- and 200-mg dose levels. Skin biopsies collected in Study JPBA predose and 4 hours postdose on Cycle 1 Day 15 show a decrease in the pRb and topoIIα expression with increasing plasma concentration. Abemaciclib effectively inhibits CDK4/6, which results in cell cycle inhibition upstream of the G1 restriction point at both doses of 150 and 200 mg.

Tumor responses were observed in patients receiving both 150 mg and 200 mg abemaciclib monotherapy. As of 29 August 2014, findings in the 47 patients with advanced or metastatic breast cancer who have been enrolled in Part D of Study JPBA resulted in 12 confirmed PRs (including 8 responses at 150 mg Q12H and 4 responses at 200 mg Q12H) among the 36 patients in Part D with HR+ mBC, based on investigators' assessment of response using RECIST v1.1. The ORR for the 36 patients in Part D with HR+ mBC was 33.3%, the DCR was 80.6%, the CBR was 61.1%, and median PFS was 8.8 months.

In a subsequent cohort of 19 patients with HR+, advanced or metastatic breast cancer enrolled in Part G of Study JPBA and treated with fulvestrant plus 200mg abemaciclib Q12H, 17 patients with abemaciclib dose reductions were observed. In addition, 4 confirmed PRs were observed for an ORR was 21.1% (36.4% in the 11 patients with measureable disease), the DCR was 78.9%, the CBR was 63.2%, and the median PFS was 10.0 months.

Preliminary safety data from Study JPBH demonstrate that the AE profile of abemaciclib administered in combination with nonsteroidal aromatase inhibitors (NSAIs) is consistent with

abemaciclib monotherapy, as the most common TEAEs possibly related to study drug were diarrhea, nausea, fatigue, and neutrophil count decreased. However, at the 200-mg dose, the incidence of treatment-emergent Grade 3 diarrhea was found to be greater when abemaciclib was administered in combination with an NSAI from a review of the preliminary safety data in Study JPBH, compared to abemaciclib administered alone in Part D of Study JPBA. Nevertheless, when the abemaciclib dose was reduced from 200 mg to 150 mg or lower for some patients in Study JPBH, either the severity of diarrhea decreased or the event resolved.

The rationale for the underlying change in the abemaciclib starting dose is, that although the Phase 1 Study JPBA demonstrated that the 200mg Q12H abemaciclib dose was tolerable when administered in combination with fulvestrant, a substantial number of patients required abemaciclib dose suspension and/or reduction during the first 2 treatment cycles. As a consequence of this observation, a review of dosing and tolerability data from patients enrolled during the first 3 months of this study was carried out as part of a regular blinded safety review to assess if a similar number of patients required dose alterations in the present study. During the review of blinded safety data from Study JPBL, any alteration in dosing of abemaciclib or placebo was presumed to have occurred on the abemaciclib arm. The data review did reveal a high number of dose alterations for abemaciclib or placebo. The cause of this was principally diarrhea occurring in the first treatment cycle. Therefore the initial dose of blinded study drug administered in combination with fulvestrant will be reduced to 150 mg Q12H.

6.1. Primary Objective

The primary objective of Study JPBL is to compare ~~LY2835219~~abemaciclib plus fulvestrant versus placebo plus fulvestrant with respect to PFS for women with HR+, HER2- locally advanced or metastatic breast cancer.

6.2. Secondary Objectives

The secondary objectives of the study are to compare ~~LY2835219~~abemaciclib plus fulvestrant versus placebo plus fulvestrant with respect to each of the following:

- overall survival (OS)
- OS rate at 1, 2, and 3 years
- objective response- rate [complete response (CR) + partial response (PR)]
- duration of response (DoR) [CR + PR]
- disease control rate (DCR) [CR + PR + stable disease (SD)]
- clinical benefit rate (CBR) [CR + PR + SD ≥6 months]
- safety and tolerability using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 4.0~~3~~)
- pain and symptom burden using the Brief Pain Inventory (BPI), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-

Core 30 (EORTC QLQ-C30) and the EORTC QLQ-BR23 (breast) questionnaires, and health status scores from the EuroQol 5-Dimension 5 Level (EQ-5D 5L)

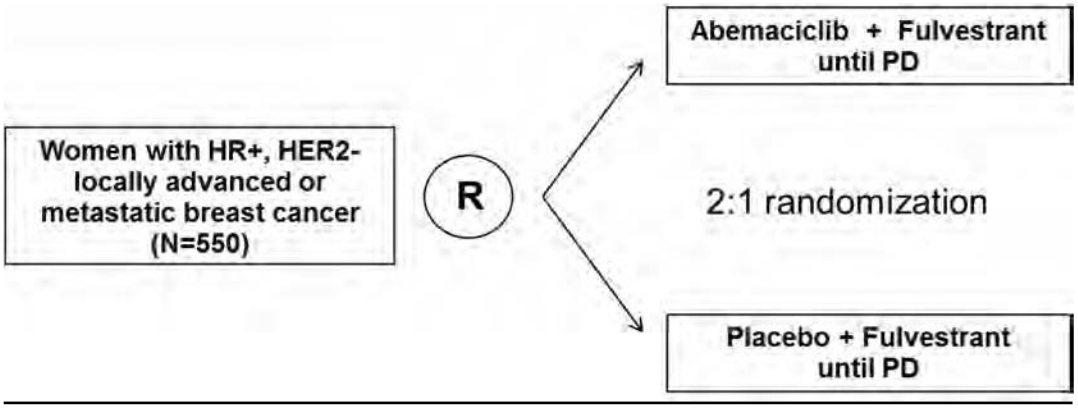
- pharmacokinetics (PK) of ~~LY2835219~~abemaciclib, its metabolites, and fulvestrant
- time to worsening of Eastern Cooperative Oncology Group (ECOG) performance status
- time to first skeletal-related event (SRE; defined as either pathological fracture, spinal cord compression, radiation to the bone, or surgery to the bone)

~~(Refer to Table JPBL.10.1. Secondary Time-to-Event Efficacy Endpoints)~~

7.1. Inclusion Criteria

[4] have a negative serum pregnancy test at baseline (within 14 days prior to randomization) and agree to use medically approved precautions to prevent pregnancy during the study and for 12 weeks following the last dose of ~~LY2835219~~abemaciclib if postmenopausal status is due to ovarian suppression with a GnRH agonist

8.1. Summary of Study Design



Abbreviations: HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2 negative; N = number; PD = progressive disease.

Figure JPBL.8.1. Illustration of study design.

Approximately 550 patients will be randomized 2:1 between the 2 arms:

- Experimental Arm A: ~~LY2835219~~abemaciclib ~~200~~ 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
- Control (Placebo) Arm B: 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

Data base lock for the interim analysis for efficacy will occur when ~~at least~~approximately 270 investigator-assessed PFS events have been observed. Database lock for the primary analysis of the PFS endpoint will occur when ~~at least~~approximately 385 investigator-assessed PFS events have been observed. All patients will be followed for progression and survival information until death or study completion, whichever occurs first.

9.1. Treatments Administered

The following treatments will be administered in this study:

- Experimental Arm A: ~~LY2835219~~Abemaciclib ~~200~~ 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
- Control (Placebo) Arm B: 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

Blinded study drug is defined as abemaciclib or placebo. Study treatment is defined as blinded study drug and fulvestrant.

Table JPBL.9.1. Treatment Regimens/Dosing Schedule

Regimen	Period/Cycle	Dose Day
Experimental Arm A		
~~LY2835219~~Abemaciclib	Treatment/28-day cycle	~~200~~ 150 mg PO Q12H on Days 1-28
Fulvestrant	Treatment/28-day cycle	500 mg IM on Days 1 and 15 of Cycle 1, then Day 1 of Cycle 2 and beyond
Control (Placebo) Arm B		
Placebo	Treatment/28-day cycle	PO Q12H on Days 1-28
Fulvestrant	Treatment/28-day cycle	500 mg IM on Days 1 and 15 of Cycle 1, then Day 1 of Cycle 2 and beyond

Abbreviations: IM = intramuscular; PO = orally; Q12H = once every 12 hours.

9.2. Materials and Supplies

~~LY2835219~~Abemaciclib or placebo (blinded study drug) will be supplied as capsules for oral administration. ~~LY2835219~~Blinded study drug capsules should be stored at room temperature according to the product label, and not opened, crushed, or dissolved. Investigators should instruct patients to store the capsules in the original package and in a location inaccessible to children. ~~LY2835219~~Blinded study drug will be labeled according to the country's regulatory requirements.

9.3. 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 ~~LY2835219~~abemaciclib plus fulvestrant or placebo plus fulvestrant. Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS.

The IWRS will be used to assign ~~LY2835219~~abemaciclib/placebo and fulvestrant (where supplied). 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.

9.4. Selection and Timing of Doses

~~LY2835219~~Blinded study drug will be taken orally every 12 (±2) hours on Days 1 through 28 of a 28-day cycle, for a total of 56 doses per cycle. Patients should not consume food beginning 1 hour before and ending 1 hour after taking ~~LY2835219~~ blinded study drug. During all cycles, ~~LY2835219~~blinded study drug should be taken at approximately the same times each day. If a patient misses or vomits a dose, that dose should be omitted.

Fulvestrant should be administered at the same time as (or up to 20 minutes after) the morning dose of ~~LY2835219~~blinded study drug, except when specified otherwise in the PK Sampling Schedule
(Attachment 7). Fulvestrant will be administered intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond. For Cycle 3 and beyond, the interval between ~~LY2835219~~blinded study drug and fulvestrant may be adjusted based on the judgment of the investigator.

A cycle is defined as the planned treatment interval of 28 days plus any subsequent delay prior to start of the next cycle. A delay in the start of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 7 days and not counted as a protocol deviation). ~~No more than 56 doses of LY2835219abemaciclib should be dispensed for each 28-day cycle.~~For each 28-day cycle, a total of 56 doses of blinded study drug will be dispensed. In exceptional cases, for planned delays (including but not limited to vacation or holidays), additional blinded study drug~~treatment~~ may be dispensed.

9.4.1.1.1.1. ~~LY2835219~~Blinded Study Drug

~~LY2835219~~Blinded study drug dose adjustments are allowed both within a cycle and between cycles. ~~LY2835219~~Blinded study drug must be reduced as outlined in Table JPBL.9.2.

Table JPBL.9.2. Dose Adjustments for ~~LY2835219~~Blinded Study Drug

Dose Adjustment	Oral Dose	Frequency
0	~~200~~ 150 mg	Q12H~~Every 12 hours~~
1	10~~5~~0 mg	Q12H
2	5~~10~~0 mg	Q12H
~~3~~	~~50 mg~~	~~Every 12 hours~~

In the event that ~~LY2835219 or placebo~~blinded study drug must be discontinued, a patient may continue to receive fulvestrant.

9.4.1.1.1.2 Fulvestrant

Dose adjustment for fulvestrant will be determined by the investigator in accordance with the label. For patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection. In the event that fulvestrant must be discontinued, a patient may continue to receive ~~LY2835219 or placebo~~blinded study drug.

9.4.1.1.2. Dose Delays

The start of a cycle may be delayed up to 14 days to allow sufficient time for recovery from toxicity possibly related to a study drug. During such a delay, ~~LY2835219/placebo~~blinded study drug and fulvestrant should not be administered. Patients not recovering from toxicity within 14 days beyond the last day of the previous~~prior~~ cycle should be considered for dose adjustment or discontinuation of the relevant study drug(s). In exceptional circumstances, a delay >14 days is permitted upon agreement between the investigator and the Lilly CRP.

In the event ~~The start~~ of a cycle delay due to~~may be delayed up to 7 days for~~ logistical reasons (for example, due to patient availability), the patient should continue on study treatment if the patient has adequate drug supply. If a patient's treatment is interrupted as a result of not having sufficient drug supply, the cycle may be delayed up to 7 days (and not considered a protocol violation). ~~During such a delay, LY2835219abemaciclib/placebo and fulvestrant should not be administered.~~ In exceptional circumstances, a delay >7 days is permitted upon agreement between the investigator and the Lilly CRP.

9.4.1.1.3. Hematologic Toxicity

If a patient experiences Grade 4 hematologic toxicity possibly related to ~~LY2835219~~blinded study drug, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 2) and the dose of ~~LY2835219~~blinded study drug must be reduced as outlined in Table JPBL.9.2.

Before the start of each cycle, hematologic toxicity possibly related to ~~LY2835219~~blinded study drug must resolve to either baseline or at least Grade 2.

9.4.1.1.4. Nonhematologic Toxicity

If a patient experiences ≥ Grade 3 nonhematologic toxicity possibly related to ~~LY2835219~~blinded study drug, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of ~~LY2835219~~blinded study drug must be reduced as outlined in Table JPBL.9.2.

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except~~such as~~ diarrhea; refer to Section 9.4.1.1.4.1) possibly related to ~~LY2835219~~blinded study drug that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, then dosing may be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of ~~LY2835219~~blinded study drug may be reduced as outlined in Table JPBL.9.2.

Before the start of each cycle, nonhematologic toxicity (except alopecia and fatigue) possibly related to ~~LY2835219~~blinded study drug must resolve to either baseline or at least Grade 1.

9.4.1.1.4.1. Diarrhea

A patient experiencing diarrhea requiring hospitalization (irrespective of grade, that is, requiring intravenous [IV] rehydration) or severe diarrhea (Grade 3 or 4; see Attachment 9) must have study treatment suspended (until the toxicity resolves to either baseline or at least Grade 1) and must have the blinded study drug dose reduced by one dose level as outlined in Table JPBL.9.2.

If a patient experiences persistent or recurrent diarrhea that does not resolve with maximal supportive measures (refer to Section 9.6.5) within 24 hours so either baseline or at least Grade 1, then study treatment should be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of blinded study drug may be reduced by one dose level as outlined in Table JPBL.9.2 at the discretion of the investigator.

9.6. Concomitant Therapy

The results from an in vitro human recombinant cytochrome P450 (CYP) phenotyping study indicate that oxidative metabolism of ~~LY2835219~~abemaciclib is primarily catalyzed by CYP3A4. However, the extent of oxidative metabolism responsible for the systemic clearance of ~~LY2835219~~abemaciclib in humans is presently unknown. Based on these in vitro findings, grapefruit juice as well as inducers (for example, phenytoin or carbamazepine) and strong inhibitors of CYP3A4 should be substituted or avoided if possible (Attachment 8). In addition, in vitro studies in primary cultures of human hepatocytes indicate that ~~LY2835219~~abemaciclib might inhibit the metabolism of CYP2B6 substrate drugs in vivo in humans. Based on this finding, bupropion and efavirenz, which are sensitive CYP2B6 substrates, should be substituted or avoided if possible.

9.6.5. ~~Therapy~~Supportive Management for Diarrhea

At randomization, patient should receive instructions on the management of diarrhea. In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

- ~~on the management of diarrhea the the s~~
- ~~diarrhea~~At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (e.g. loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours
- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours to either baseline or Grade 1, blinded study drug should be suspended until diarrhea is resolved to baseline or Grade 1.
- When blinded study drug recommences dosing should be adjusted as outlined in Section 9.4.1.1.1.1 and Table JPBL.9.2.

In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

Patients with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid (IV hydration) and electrolyte replacement. ~~For diarrhea, at the first sign of loose stools, initiation of treatment with antidiarrheal agents (for example, loperamide) is recommended. For patients with persistent diarrhea, refer to the dose adjustment guidelines in Section 9.4.1.1.1.1.~~

10.2.1. Patient-Reported Outcomes

The primary health outcomes research goal is to determine if ~~LY2835219~~abemaciclib combination therapy is able to palliate pain, as measured by the mBPI-sf (Cleeland 1991). Additionally, the EORTC QLQ-C30 (Aaronson et al. 1993) will assess the broader impact of ~~LY2835219~~abemaciclib combination therapy on quality of life, the EORTC QLQ-BR23 (Sprangers et al. 1996) will collect disease-specific data, and the EQ-5D 5L (Janssen et al. 2008) health status assessment will allow for comparison with other tumor types and disease states.

10.2.1.3. Health Status

The EQ-5D 5L is designed to be used in conjunction with other patient-reported measures. Patients will complete the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment according to the Study Schedule (Attachment 1). A visual analog scale (VAS) "thermometer" measures current health state. ~~EQ-5D-5L responses may be incorporated into cost utility analyses, but will not be included in the clinical study report.~~

10.3.4. Complaint Handling

Complaints related to fulvestrant or the prefilled fulvestrant syringes should be reported directly to the manufacturer in accordance with the package insert.

Complaints related to ~~LY2835219~~blinded study drug should be reported directly to Lilly.

10.4.2.1. Archived Tumor Tissue

For patients in the study, a small amount of preserved tumor tissue, previously taken to evaluate the patient's disease, should be requested for biomarker research. Formalin-fixed paraffin-embedded tumor tissue should be in a whole block, partial block, or unstained slides. Any whole block submitted will be returned to the site. Any partial blocks or slides will either be returned or discarded within 15 years after last patient visit for the trial.

In tumor tissue samples, the CDK4/6 pathway components (for example, Rb) and markers relevant breast cancer pathogenesis may be evaluated to assess any potential correlation with response to ~~LY2835219~~abemaciclib. Tumor samples may be analyzed to explore potential tumor gene signature(s) associated with response or resistance to ~~LY2835219~~abemaciclib

therapy. These studies may be analyzed at a laboratory designated by the sponsor and may include IHC of proteins, FISH for copy number amplifications, RNA gene-expression profiling, and/or genetic analyses of the tumor specimen DNA. Such analyses may employ targeted or high-throughput sequencing approaches. For this purpose, the results of this analysis will be correlated with clinical efficacy data.

10.4.2.2. Blood Samples for Pharmacogenetic Evaluations

Where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis. Samples may be genotyped and analysis may be performed to evaluate a genetic association with response to ~~LY2835219~~abemaciclib. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response.

10.4.2.3. Plasma Samples for Exploratory Biomarker Evaluations

Plasma samples will be collected and analysis may be performed on biomarkers that may play a role in the ~~LY2835219~~abemaciclib mechanism of action (refer to Attachment 1). The evaluation of these samples may involve analysis of DNA, RNA, and proteins (including any of these components derived from exosomes) to investigate their association with observed clinical outcomes to study drug.

10.4.3. Samples for Drug Concentration Measurements Pharmacokinetics

At the visits and times specified in the Pharmacokinetic Sampling Schedule (Attachment 7), venous blood samples of approximately 4 mL each will be collected to determine the plasma concentrations of ~~LY2835219~~abemaciclib and its metabolites LSN2839567, LSN3106726, and LSN3106729, as well as plasma concentrations of fulvestrant.

Separate blood samples are not required for the parent, its metabolites, and fulvestrant. After obtaining plasma, samples will be aliquoted into 2 approximately equal portions by site personnel, one for the determination of plasma concentrations of ~~LY2835219~~abemaciclib and its metabolites and the other for the determination of plasma concentrations of fulvestrant. Instructions for the collection and handling of blood samples will be provided by the sponsor. It is preferred that the blood samples be obtained from a peripheral location.

These samples will be analyzed at a laboratory designated by the sponsor. Plasma concentrations of ~~LY2835219~~abemaciclib plus its metabolites LSN2839567, LSN3106726, and LSN3106729 will be assayed using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

12.1. Determination of Sample Size

The primary objective of this study is to compare ~~LY2835219~~abemaciclib plus fulvestrant versus placebo plus fulvestrant in terms of PFS for women with HR+, HER2- locally advanced or metastatic breast cancer.

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 Section 12.2.6 for details). The

primary PFS analysis will be performed after 385 PFS events have occurred (that is, a 30% censoring rate). Assuming a hazard ratio (HR) of 0.703, this sample size yields at least 90% statistical power to detect superiority of the ~~LY2835219~~abemaciclib plus fulvestrant arm over the placebo plus fulvestrant 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 fulvestrant arm is 6.5 months, then the HR of 0.703 amounts to an approximately 2.75-month (42%) improvement in median PFS for the ~~LY2835219~~abemaciclib plus fulvestrant arm under an additional assumption of exponential survival distribution. Assuming approximately 10% screening failure, the study will enter approximately 600 patients.

12.2.1. General Considerations

Safety analyses will be based on the Safety Population, defined as all enrolled patients receiving at least 1 dose of blinded ~~any~~ study drug or fulvestrant. Patients will be grouped according to treatment received in Cycle 1.

12.2.5. Treatment Compliance

Treatment compliance information for ~~LY2835219~~blinded study drug will be collected through capsule counts at each tumor assessment visit. The estimate of percent compliance will be given by:

$$\text{Percent Compliance} = \frac{\text{Actual cumulative dose taken}}{\text{Expected cumulative dose to be taken}} \text{ x } 100$$

12.2.6. Primary Outcome and Methodology

The PFS analysis to test the superiority of ~~LY2835219~~abemaciclib to placebo in improving PFS time will use the log-rank test stratified by nature of disease (visceral metastases versus bone only metastases versus other) and sensitivity to endocrine therapy (no prior endocrine therapy versus primary resistance versus secondary resistance). In addition, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the PFS curves as well as PFS rates at every 3 months for each treatment group.

12.2.7. Secondary Outcome and Methodology

The OS analysis to test the superiority of ~~LY2835219~~abemaciclib to placebo in improving OS time will use the log-rank test stratified by nature of disease (visceral metastases versus bone only metastases versus other) and sensitivity to endocrine therapy (no prior endocrine therapy versus primary resistance versus secondary resistance).

12.2.9. Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetics analyses will be conducted on all patients who have received at least 1 dose of ~~LY2835219~~abemaciclib and have had samples collected (see PK sampling schedule in Attachment 7).

Mean population PK parameters for ~~LY2835219~~abemaciclib and its metabolites in plasma (clearance, exposure, volume of distribution, and half-lives) and inter-individual PK variability

will be computed using nonlinear mixed effect modeling implemented in NONMEM. The current PK model for ~~LY2835219~~abemaciclib, which has been developed using plasma concentration data available from the Phase 1 Study JPBA, will be updated using the plasma data collected in this study. Covariate effects (such as age, weight, sex, creatinine clearance, and plasma protein levels) on the PK parameters of ~~LY2835219~~abemaciclib in plasma will also be investigated.

If warranted by the data, mean population PK parameters for fulvestrant in plasma and inter-individual variability estimates will also be computed using nonlinear mixed effect modeling implemented in NONMEM.

Finally, pharmacodynamic data (such as neutrophil, lymphocytes, or platelets counts in blood) collected in this study may be analyzed by means of NONMEM and connected to the population PK model for ~~LY2835219~~abemaciclib and/or fulvestrant in a PK/pharmacodynamic model.

12.2.12. Safety Analyses

AEs will be reported using a unified CTCAE/MedDRA reporting process:

- The CTCAE v4.0~~3~~ term reported by the investigator will be mapped to the MedDRA Preferred Term (PT) and System Organ Class (SOC) of the corresponding MedDRA Lower Level Term (LLT), unless the reported CTCAE term is 'Other – specify'.

12.2.14.1. Safety Interim Analyses

During the study, safety interim analyses will be performed every 3 months. The first safety interim analysis will be triggered by the 90th patient enrolling, with the data cutoff for this analysis occurring 1 month after the trigger. The safety interim analyses will be conducted to evaluate the overall safety profile of ~~LY2835219~~abemaciclib when given in combination with fulvestrant. At the recommendation of the DMC, the frequency of safety interim analyses may be modified.

Attachment 1. Protocol JPBL Study Schedule

			Baseline		Patients on Study Treatment				Postdiscontinuation Follow-Up	
		Cycle	BL		1		2 – 3	4 and Beyond (if Applicable)	Short-Term Follow-Up[a]	Long-Term Follow-Up[a]
		Visit	0		1		2 – 3	4 and Beyond (if Applicable)	801	802 - 8XX
		Approximate Duration (days)	28		28		28	28	30	Variable
		Relative day within a cycle	≤28	≤14	1	15±3	1[p]	1[p]		
Procedure Category	**Procedure**	**Protocol Reference**								
Study Drug	Fulvestrant Therapy [g]	Section 9.1			Days 1 and 15 of Cycle 1, then Day 1 of Cycle 2 and beyond[g]					
	~~LY2835219~~Abemaciclib or Placebo Therapy[g]	Section 9.1			~~Every~~Q12~~hours~~H on Days 1 through 28 of every cycle[g]					
Health Outcomes	BPI, EORTC QLQ-C30, EORTC BR23, EQ-5D 5L[k]	Section 12.2.11		X[k]			X[k]	X[k]	X[k]	
	Skeletal-Related Events assessment[l]	Section 12.2.11		X[l]			X[l]	X[l]	X[l]	X[l]
	Hospitalization	Section 12.2.11.4		X			X	X	X	
	Transfusion	Section 12.2.11.4		X			X	X	X	

Abbreviations: BL = baseline; Temp = Temperature; BP = Blood Pressure; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; GnRH = gonadotropin-releasing hormone; HR = heart rate; IV = intravenous; PK = pharmacokinetics; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; Q12H = every 12 hours; SAEs = serious adverse events; FSH = follicular stimulating hormone.

g ~~LY2835219~~Blinded study drug should be administered orally ~~every~~Q12~~hours~~H on Days 1 through 28 of each cycle; patients should not consume food beginning 1 hour before and ending 1 hour after taking ~~LY2835219~~blinded study drug. Fulvestrant 500 mg should be administered intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock; however, for patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection.

Study Schedule for the extension period only, Protocol I3Y-MC-JPBL

Perform procedure as indicated.

			Patients on Study Treatment		Extension Period Follow-Up
		Cycle	X-Y		Follow-Up[a]
		Visit	501-5XX		901
		Duration (days)	28		30
		Relative day within a cycle	1	15	
Procedure Category	**Procedure**	**Protocol Reference**			
Adverse Events Collection/CTCAE Grading[b]		Section 10.3	X		X
Study Drug	Fulvestrant Therapy[c]	Section 8.1.2	Days 1 and 15 of Cycle 1, then Day 1 of Cycle 2 and beyond[c]		
	~~LY2835219~~Abemaciclib Therapy[c]	Section 8.1.2	Daily ~~every~~Q12~~hours~~H[c]		

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; PK = pharmacokinetics; Q12H = every 12 hours; SAEs = serious adverse events.

a The extension period begins after study completion and ends at the end of trial.

b Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system.

c ~~LY2835219~~Abemaciclib should be administered ~~every~~Q12~~hours~~H on Days 1 through 28 of each cycle. Patients should not consume food beginning 1 hour before and ending hour after taking study drug.

Fulvestrant 500 mg should be administered intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock; however, for patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection.

Attachment 3. Protocol JPBL Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented and bands	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 6. Protocol JPBL Sampling Summary

This table summarizes the purpose for sampling, sample types, maximum volume per sample, maximum number of samples, and maximum total volume during the study. The summary below provides estimates. More samples could be required in the case of retests ~~Protocol~~, additional health monitoring (if needed), or for patients continuing treatment beyond the protocol-specified number of cycles in the study. Fewer samples may actually be taken (for example, patients who discontinue from the study).

Attachment 7 Protocol JPBL Pharmacokinetic Sampling Schedule

The schedule for PK sampling is summarized in the table below. The date and exact time of collection for each venous blood sample should be documented on the laboratory requisition.

Pharmacokinetic Sampling Schedule

PK Sample Number	Cycle (C) and Day (D)	Dosing of ~~LY2835219~~Abemaciclib or Placebo (Blinded Study Drug)	Dosing of Fulvestrant	Sampling Time for PK from Blood[a]
1	C1D1	X	X	2 to 4 hrs after fulvestrant and ~~LY~~blinded study drug dose
2	C1D15	X[b]	X	Upon arrival at site but prior to fulvestrant dose (that is, at least 4 hrs after taking ~~LY~~blinded study drug dose at home)
3	C1D15			3 ± 0.5 hrs after PK Sample Number 2 (that is, at least 7 ± 0.5 hrs after taking ~~LY~~blinded study drug dose at home)
4	C2D1	X	X	Prior to fulvestrant and ~~LY~~blinded study drug dose
5	C2D1			3 ± 0.5 hrs after ~~LY~~blinded study drug dose
6	C3D1	X	X	Prior to fulvestrant and ~~LY~~blinded study drug dose

Abbreviations: hr = hour~~; LY = LY2835219~~; PK = pharmacokinetic.

a Samples of approximately 4 mL of whole blood will be drawn. After obtaining plasma, site personnel will aliquot samples into 2 approximately equal portions, one for measurement of LY2835219 and its metabolites concentrations and the other for measurement of fulvestrant concentrations. Only samples No. 1, 2, 4, and 6 will be used for measurement of fulvestrant.

b On Cycle 1 Day 15 only, patient should take ~~LY~~blinded study drug dose at home at least 4 hours before arrival at site. The time of ~~LY~~blinded study drug dose intake must be recorded that day.

Attachment 9. Protocol JPBL CTCAE 4.03 Diarrhea Definition

Diarrhea will be evaluated in this study using the criteria proposed by Common Terminology Criteria for Adverse Events (CTCAE) v4.0 revised: CTCAE 4.03-June 14, 2010: Gastrointestinal disorders.

Gastrointestinal Disorders					
Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase <= 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: a disorder characterized by frequent and watery bowel movements					

Abbreviation: ADL = Activities of Daily Living.

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