Protocol I3Y-MC-JPCF(e)

A Randomized, Open-Label, Phase 3 Study of Abemaciclib Combined with Standard Adjuvant Endocrine Therapy versus Standard Adjuvant Endocrine Therapy Alone in Patients with High Risk, Node Positive, Early Stage, Hormone Receptor Positive, Human Epidermal Receptor 2 Negative, Breast Cancer

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Abemaciclib (LY2835219)

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1. Synopsis

Protocol Title: A Randomized, Open-Label, Phase 3 Study of Abemaciclib combined with Standard Adjuvant Endocrine Therapy versus Standard Adjuvant Endocrine Therapy Alone in Patients with High Risk, Node Positive, Early Stage, Hormone Receptor Positive, Human Epidermal Receptor 2 Negative, Breast Cancer

Rationale: Study I3Y-MC-JPCF (JPCF; monarchE) is a Phase 3 study for patients with node-positive, early stage, hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer who completed definitive locoregional therapy (with or without neoadjuvant or adjuvant chemotherapy) and are at high risk for disease recurrence. The currently approved standards of care offered to this patient population are adjuvant cytotoxic chemotherapy and endocrine therapy. Despite advances in therapeutic options for early stage breast cancer, a high-risk subpopulation receives suboptimum benefit and may demonstrate resistance to anti-estrogen therapy at the time of recurrence. Therefore, improving the absolute benefit of adjuvant endocrine therapy is warranted in this high-risk subgroup given its cumulative rate of disease recurrence at 5 years is at least 15%. This Phase 3 study will evaluate the potential for abemaciclib to enhance standard adjuvant endocrine therapy compared to standard adjuvant endocrine therapy alone in patients with node-positive, early stage, resected HR+, HER2- breast cancer at high risk of disease recurrence.

Objectives and Endpoints:

Primary Objective:

- To evaluate the efficacy, in terms of invasive disease-free survival (IDFS), as defined by the STEEP System, for patients with HR+, HER2- early stage breast cancer for abemaciclib 150 mg twice daily plus adjuvant endocrine therapy versus adjuvant endocrine therapy alone

Secondary Objective:

- To evaluate the efficacy, in terms of IDFS, for patients with HR+, HER2- early stage breast cancer with Ki-67 index ≥20% by central lab
- To evaluate the efficacy of abemaciclib plus adjuvant endocrine therapy versus adjuvant endocrine therapy alone in terms of distant relapse-free survival (DRFS) and overall survival (OS)
- To assess the safety profile of abemaciclib plus adjuvant endocrine therapy compared to adjuvant endocrine therapy alone
- To evaluate the relationship between abemaciclib exposure and clinical (efficacy and safety) outcomes
- To evaluate abemaciclib plus adjuvant endocrine therapy, versus adjuvant endocrine therapy alone, in terms of general oncology and breast cancer self-reported health-related quality of life (Functional Assessment of Cancer Therapy [FACT]-Breast 37-item questionnaire), endocrine therapy-specific symptoms (Functional Assessment of Cancer Therapy - Endocrine Symptoms (Version 4) [FACT-ES] 19-item subscale and 2

Functional Assessment of Chronic Illness Therapy Item Library [FACIT] (Version 2) sourced items of cognitive symptoms and 3 FACIT-sourced items for bladder symptoms), and fatigue experienced during abemaciclib and/or endocrine therapy (FACIT-Fatigue 13-item subscale)

- To evaluate health status to inform decision modeling for health economic evaluation using the EuroQol five-dimension five-level questionnaire (EQ-5D-5L)

Overall Design: monarchE is a multicenter, randomized, open-label, Phase 3 study of standard adjuvant endocrine therapy of physician's choice with or without abemaciclib in patients with high-risk, node-positive, early stage, HR+, HER2- breast cancer, who completed definitive locoregional therapy (with or without neoadjuvant or adjuvant chemotherapy).

Number of Patients: The study will screen approximately 5200 patients, and approximately 4580 patients will be enrolled and subdivided into 2 cohorts: those eligible based on nodal status, tumor size, or grade regardless of Ki-67 status (Cohort 1) and those with at least 1 positive node and eligible exclusively based on a Ki-67 status (Cohort 2, patients not eligible based on degree of axillary lymph node involvement, tumor size or grade).

Study Design: Patients in both treatment arms will receive standard adjuvant endocrine therapy of physician's choice (such as tamoxifen or an aromatase inhibitor, with or without ovarian function suppression per standard practice). Patients in both arms may have up to 12 weeks of endocrine therapy following their last non-endocrine therapy (surgery, chemotherapy, or radiotherapy) prior to randomization, and the same or another endocrine therapy will be continued during the course of the study until meeting discontinuation criteria (Section 8). Adjuvant treatment with fulvestrant is not allowed at any time during the study. Patients must be randomized within 16 months of definitive breast surgery for the current malignancy. Patients randomized to the experimental arm will receive abemaciclib orally at 150 mg twice daily for up to 2 years or until discontinuation criteria are met, whichever occurs first. Endocrine therapy will be taken as prescribed during the on-study treatment period (Years 1 and 2). In Year 3 and beyond, standard adjuvant endocrine therapy will continue to complete at least 5 years per investigator's discretion as part of standard of care.

2. Schedule of Activities

The screening period for Cohort 1 is 3 months. The screening period for Cohort 2 is 6 months (tissue for Cohort 2 patients should be submitted within one month from the consent date).

In both Arms A and B, Day 1 is the first dose of treatment following randomization, that is, abemaciclib and/or endocrine therapy (Arm A), or endocrine therapy (Arm B), regardless if the patient is receiving endocrine therapy immediately prior to randomization. The first dose of abemaciclib and/or endocrine therapy should be initiated no later than 3 days following randomization.

During Years 1 and 2 (the on-study treatment period), patients will return to clinic every 2 weeks (15 ± 3 days) for the first 2 months, monthly (30 ± 5 days) starting with Month 3 to Month 6, and every 3 months thereafter (every 90 ± 10 days until Visit 27). Phone visits will happen monthly between the every 3 month visits.

All visits will be anchored to the previous clinic visit, with the exception of Visit 27. Visit 27 must be anchored to Visit 1 and must take place 24 months (±5 days) after Visit 1. Unscheduled visits must be scheduled to complete the 2-year period between Visit 26 and Visit 27 if there are >40 days between Visit 26 and Visit 27. These unscheduled visits should include assessments applicable for either a clinic visit (if the visit is happening in the clinic) or phone visit (if the visit is happening on the phone) using the schedule of assessments below as the guide.

For patients enrolled in Arm B who are unable to attend the required clinic visits, Visits 2, 4, 5, 7, and 8 must take place as a phone visit if the clinic visit cannot be done.

Detection of symptoms suspicious of disease recurrence is highly important. The investigator or another medically qualified individual is expected to conduct a comprehensive and systematic assessment of these symptoms during clinic and phone visits. Of note, the protocol does not prohibit more frequent monitoring by imaging, if judged necessary by the investigator.

The short-term follow-up visit takes place 30 days (±5 days) after 1 of the following time points, whichever occurs first:

- after the completion of the 2-year on-study treatment period
- after discontinuation criteria are met (Section 8.1) and decision is made for the patient to discontinue all study treatment (abemaciclib plus endocrine therapy in Arm A, endocrine therapy in Arm B) prior to the completion of the 2-year on-study treatment period

Note: For Arm A only, if a patient discontinues only one of the combination drugs (abemaciclib or endocrine therapy) prior to completion of the 2-year on-study treatment period for a reason other than an IDFS event per STEEP criteria (Appendix 10), she/he should continue the other drug until completion of the 2-year on-study treatment period or other discontinuation criteria are met (Section 8.1), whichever occurs first.

After the short-term follow-up visit, ALL patients will enter the long-term follow-up period (see Table JPCF.2.1). The long-term follow-up period begins the day after the short-term follow-up

visit and will continue up to Year 10 or study completion, whichever occurs first. Long-term follow-up visits should occur approximately every 6 months (anchored to the previous visit) until the completion of Year 5, and then yearly starting in Year 6. For patients who are unable to attend the required clinic visits, long-term follow-up visits V803 and further must take place as a phone visit if the clinic visit cannot be done.

If a patient experiences an IDFS event other than distant recurrence or death, she/he will be followed for distant recurrence and survival, unless the patient is lost to follow-up, or withdraws from the study.

Unscheduled visits (V997) and all procedures for the unscheduled visits are at the discretion of the investigator. Unscheduled visits may include physical examinations, vital signs, ECOG performance status, concomitant medication, adverse event collection, disease symptoms assessment, central chemistry and hematology, return of study drug, or resumed dosing, if previously interrupted.

The windows for the schedule of assessments and administration of first dose are based on calendar days.

Table JPCF.2.1. Schedule of Activities

Study Period	Screening			On-Study Treatment Period (Y1-2)				Short-Term Follow-Up	Long-Term Follow-Up	Comments
Day (relative to Visit 1)	**−6 M to R**	**−28 to R**	**−14 to R**	**Day 1 (R+≤3D)**	**Q2W (M1-2) (±3D)**	**Monthly (M3-6) (±5D)**	**Monthly (M7-Y2) (±5D)***	**30 Days post DC (±5D)**	**Q6M then Q12M (±28D)**	**Clinic visits: 1-9, 12, 15, 18, 21, 24, 27** Phone visits: 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26 LTFU: Q6M through Y5; Q12M Y6-10. *3 monthly clinic visits ± 10 days
Visit	**601 Cohort 2 only**	**0**		**1**	**2-5**	**6-9**	**10-27**	**801**	**≥802**	
Informed consent (Cohort 2 and/or main consent)	X	X								Main ICF may be signed up to 3 months prior to randomization and must be signed prior to any study-specific assessments are performed. Cohort 2 ICF may be signed up to 6 months prior to randomization and must be signed prior to sending tissue to the central lab for Ki-67 testing.
Blood pregnancy test			X							See inclusion criteria [12], Appendix 4. Women of reproductive potential only. Local regulations and/or institutional guidelines may require additional testing.

Study Period	Screening			On-Study Treatment Period (Y1-2)				Short-Term Follow-Up	Long-Term Follow-Up	Comments
Day (relative to Visit 1)	**−6 M to R**	**−28 to R**	**−14 to R**	**Day 1 (R+≤3D)**	**Q2W (M1-2) (±3D)**	**Monthly (M3-6) (±5D)**	**Monthly (M7-Y2) (±5D)***	**30 Days post DC (±5D)**	**Q6M then Q12M (±28D)**	**Clinic visits: 1-9, 12, 15, 18, 21, 24, 27** Phone visits: 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26 LTFU: Q6M through Y5; Q12M Y6-10. *3 monthly clinic visits ± 10 days
Visit	**601 Cohort 2 only**	**0**		**1**	**2-5**	**6-9**	**10-27**	**801**	**≥802**	
Physical exam (clinic visits only)		X		(X)	X	X	X	X	X	Height, weight, and appropriate body examination. Height at baseline only and weight until STFU. Does not need to be repeated on Day 1 if assessed ≤7 days prior to randomization.
Vital signs (clinic visits only)		X		(X)	X	X	X	X		Blood pressure, pulse, respiratory rate, temperature. Do not need to be repeated on Day 1 if assessed ≤7 days prior to randomization.
ECOG PS (clinic visits only)		X		(X)	X	X	X	X		See Appendix 11. Does not need to be repeated on Day 1 if assessed ≤7 days prior to randomization.
Medical history		X								Includes alcohol and tobacco intake.
Concomitant medications		X		X	X	X	X	X	X	In LTFU, collection of regimen changes and associated start and stop dates for endocrine therapy, and post-discontinuation therapy.
ECG (local)			X	As clinically indicated						Patient must be supine or near supine for approximately 5-10 minutes prior to collection and remain supine, but awake, during collection.

Study Period	Screening			On-Study Treatment Period (Y1-2)				Short-Term Follow-Up	Long-Term Follow-Up	Comments
Day (relative to Visit 1)	**−6 M to R**	**−28 to R**	**−14 to R**	**Day 1 (R+≤3D)**	**Q2W (M1-2) (±3D)**	**Monthly (M3-6) (±5D)**	**Monthly (M7-Y2) (±5D)***	**30 Days post DC (±5D)**	**Q6M then Q12M (±28D)**	**Clinic visits: 1-9, 12, 15, 18, 21, 24, 27** Phone visits: 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26 LTFU: Q6M through Y5; Q12M Y6-10. *3 monthly clinic visits ± 10 days
Visit	**601 Cohort 2 only**	**0**		**1**	**2-5**	**6-9**	**10-27**	**801**	**≥802**	
Adverse event assessment		X		X	X	X	X	X	X	See Section 9.2. Assessments will be in clinic and over the phone between clinic visits. In LTFU, all SAEs in both arms regardless of causality will be collected through Year 5. For the entire duration of LTFU, only AEs related to study treatment and/or study procedure will be collected.
Central hematology, chemistry, and cystatin C (clinic visits only)			X	(X)	X	X	X	X		See Appendix 3. Do not need to be repeated on Day 1 if assessed ≤7 days prior to randomization (blood draw is required at Day 1 for pharmacogenetic and biomarker sample collection – see Appendix 6). Eligibility must be based on the last available screening laboratory results prior to randomization. Enrollment and treatment decisions may be based on local laboratory results, but a specimen must also be sent to central laboratory. Discrepancies between local and central laboratory results will not be considered protocol deviations.

Study Period	Screening			On-Study Treatment Period (Y1-2)				Short-Term Follow-Up	Long-Term Follow-Up	Comments
Day (relative to Visit 1)	**−6 M to R**	**−28 to R**	**−14 to R**	**Day 1 (R+≤3D)**	**Q2W (M1-2) (±3D)**	**Monthly (M3-6) (±5D)**	**Monthly (M7-Y2) (±5D)***	**30 Days post DC (±5D)**	**Q6M then Q12M (±28D)**	**Clinic visits: 1-9, 12, 15, 18, 21, 24, 27** Phone visits: 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26 LTFU: Q6M through Y5; Q12M Y6-10. *3 monthly clinic visits ± 10 days
Visit	**601 Cohort 2 only**	**0**		**1**	**2-5**	**6-9**	**10-27**	**801**	**≥802**	
PRO questionnaires				X		V6, V9	V15, V21, V27	X	V802, V803	See Section 9.9.
Bilateral breast imaging (such as mammogram or MRI)		Prior to randomization: Patients must have bilateral breast imaging performed locally as part of routine standard of care prior to surgery or prior to randomization for the current breast cancer. This is not required for patients who have had bilateral mastectomy. Post randomization: Either at yearly intervals, as recommended per international standard guidelines, or according to local standards as part of routine medical care. Patients who have had a mastectomy should be followed per local practice. See Appendix 10 for additional guidelines for the assessment of recurrence.								
Abdominal ± pelvic imaging (such as CT, PET/CT, MRI, ultrasound)		Prior to randomization: Abdominal ± pelvic imaging MUST be performed prior to randomization. Abdominal ± pelvic imaging performed previously as part of routine care, any time in the process of or after diagnosing the patient with the current breast cancer diagnosis, may be used as the baseline assessment. Post randomization: Performed locally ONLY if clinically indicated per investigator's judgment (eg, if liver function tests deteriorate significantly). If PET/CT is performed, additional imaging modalities are not required. See Appendix 10 for additional guidelines for the assessment of recurrence.								
Chest imaging (such as PET/CT, CT, or x-ray [should include lateral and postero-anterior views])		Prior to randomization: Chest imaging MUST be performed prior to randomization. Chest imaging performed previously as part of routine care, any time in the process of or after diagnosing the patient with the current breast cancer diagnosis, may be used as the baseline assessment. Post randomization: Performed locally ONLY if clinically indicated per the investigator's judgment. If PET/CT is performed, additional imaging modalities are not required. See Appendix 10 for additional guidelines for the assessment of recurrence.								

Study Period	Screening			On-Study Treatment Period (Y1-2)				Short-Term Follow-Up	Long-Term Follow-Up	Comments
Day (relative to Visit 1)	**−6 M to R**	**−28 to R**	**−14 to R**	**Day 1 (R+≤3D)**	**Q2W (M1-2) (±3D)**	**Monthly (M3-6) (±5D)**	**Monthly (M7-Y2) (±5D)***	**30 Days post DC (±5D)**	**Q6M then Q12M (±28D)**	**Clinic visits: 1-9, 12, 15, 18, 21, 24, 27** Phone visits: 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26 LTFU: Q6M through Y5; Q12M Y6-10. *3 monthly clinic visits ± 10 days
Visit	**601 Cohort 2 only**	**0**		**1**	**2-5**	**6-9**	**10-27**	**801**	**≥802**	
Bone nuclear imaging (such as bone scan, PET scan or PET/CT)		Prior to randomization: Full body bone imaging per standard clinical practice MUST be performed prior to randomization to discard or confirm potential distant disease. Bone imaging performed previously as part of routine care, any time in the process of or after diagnosing the patient with the current breast cancer diagnosis, may be used as the baseline assessment. Post randomization: Performed locally and ONLY if clinically indicated per investigator's judgment (for example, if patient is symptomatic for bone pain and/or if alkaline phosphatase is significantly elevated ≥3×ULN). If PET/CT is performed, additional imaging modalities are not required. See Appendix 10 for additional guidelines for the assessment of recurrence.								
Administer abemaciclib (Arm A)				At all clinic visits						See Sections 7.1 and 7.7.1.1. Orally twice-daily (with minimum 6-hour separating doses) for up to 2 years or until discontinuation criteria met.
Administer endocrine therapy				As per standard of care				(X)	(X)	See inclusion criterion [7] In STFU and LTFU, as applicable. Administered as per physician's choice.
Disease recurrence assessment					At every visit and as clinically indicated until distant disease recurrence or death					See Section 9.1 and Appendix 10. Disease recurrence information will be collected at any time point (clinic or phone visit). Assessment for changes in symptoms and suggestive of disease recurrence.

Study Period	Screening			On-Study Treatment Period (Y1-2)				Short-Term Follow-Up	Long-Term Follow-Up	Comments
Day (relative to Visit 1)	**−6 M to R**	**−28 to R**	**−14 to R**	**Day 1 (R+≤3D)**	**Q2W (M1-2) (±3D)**	**Monthly (M3-6) (±5D)**	**Monthly (M7-Y2) (±5D)***	**30 Days post DC (±5D)**	**Q6M then Q12M (±28D)**	**Clinic visits: 1-9, 12, 15, 18, 21, 24, 27** Phone visits: 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26 LTFU: Q6M through Y5; Q12M Y6-10. *3 monthly clinic visits ± 10 days
Visit	**601 Cohort 2 only**	**0**		**1**	**2-5**	**6-9**	**10-27**	**801**	**≥802**	
Ki-67 tissue (untreated breast tissue)	X									See Section 9.8.1 and Appendix 6. As assessed by central laboratory when kit is available for both cohorts. Screening for potential Cohort 2 patients is permitted after signing the Cohort 2 ICF ((tissue should be submitted within 1 month from consent date).
Ki-67 and exploratory biomarker tissue (post-neoadjuvant therapy)	X									See Section 9.8.1 and Appendix 6. In addition to pretreatment sample, if available, send to central laboratory only for patients who received neoadjuvant therapy. Not applicable for patients who had a pCR following neoadjuvant therapy.

Study Period	Screening			On-Study Treatment Period (Y1-2)				Short-Term Follow-Up	Long-Term Follow-Up	Comments
Day (relative to Visit 1)	**−6 M to R**	**−28 to R**	**−14 to R**	**Day 1 (R+≤3D)**	**Q2W (M1-2) (±3D)**	**Monthly (M3-6) (±5D)**	**Monthly (M7-Y2) (±5D)***	**30 Days post DC (±5D)**	**Q6M then Q12M (±28D)**	**Clinic visits: 1-9, 12, 15, 18, 21, 24, 27** Phone visits: 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26 LTFU: Q6M through Y5; Q12M Y6-10. *3 monthly clinic visits ± 10 days
Visit	**601 Cohort 2 only**	**0**		**1**	**2-5**	**6-9**	**10-27**	**801**	**≥802**	
Tumor tissue for biomarkers		X								See Section 9.8 and Appendix 6. Confirm sample availability prior to randomization. Breast tissue preferred; lymph node tissue is acceptable. For patients who received neoadjuvant therapy, send both a pre- and a post–neoadjuvant treatment tissue sample to the central laboratory (unless the patient had a pCR).
Plasma for biomarker				X		V6, V9	V27		V802, Y5	See Section 9.8 and Appendix 6. At Day 1, must be taken before first dose. V802 sample may be taken after V802 if missed at V802. Y5 sample for patients on study without IDFS event
Pharmacokinetics				X	V3, V5	V6				Only for patients in Arm A assigned to PK in IWRS. See Section 9.5 and Appendix 6. Ask the patient and record date and time of last abemaciclib dose prior to PK sample. V1 sample, 2 hours after abemaciclib dosing. Other visits, any time after abemaciclib dosing.

Study Period	Screening			On-Study Treatment Period (Y1-2)				Short-Term Follow-Up	Long-Term Follow-Up	Comments
Day (relative to Visit 1)	**−6 M to R**	**−28 to R**	**−14 to R**	**Day 1 (R+≤3D)**	**Q2W (M1-2) (±3D)**	**Monthly (M3-6) (±5D)**	**Monthly (M7-Y2) (±5D)***	**30 Days post DC (±5D)**	**Q6M then Q12M (±28D)**	**Clinic visits: 1-9, 12, 15, 18, 21, 24, 27** Phone visits: 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26 LTFU: Q6M through Y5; Q12M Y6-10. *3 monthly clinic visits ± 10 days
Visit	**601 Cohort 2 only**	**0**		**1**	**2-5**	**6-9**	**10-27**	**801**	**≥802**	
Whole blood for pharmacogenetic analysis				X						See Appendix 6. Whole blood sample required.
Recurrence tissue and plasma samples (biomarker)				Collect at time of local/regional and distant disease recurrence						See Section 9.8 and Appendix 6. Tissue sample mandatory for patients who undergo biopsy to confirm recurrence.
Survival				X						

Abbreviations: CRF = case report form; CT = computed tomography; D = day; DC = discontinuation; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ICF = informed consent form; IWRS = interactive web-response system; LTFU = long-term follow-up; M = month(s); MRI = magnetic resonance imaging; pCR = pathological complete response; PET = positron emission tomography; PK = pharmacokinetics; PRO = patient-reported outcomes; Q2W = every 2 weeks; Q6M = every 6 months; Q12M = every 12 months; R = randomization; SAE = serious adverse event; STFU = short-term follow-up; V = visit; Y= year.

3. Introduction

3.1. Disease Background

Breast cancer is the most frequent cancer among women and is a major cause of cancer-related deaths worldwide. It is estimated that more than 1.67 million new cases of breast cancer occurred worldwide in women in 2012 (Ferlay et al. 2015). In the United States, breast cancer is the most common malignancy diagnosed among women, and the second leading cause of cancer deaths in women, with 246,660 new cases of invasive breast cancer and 40,450 deaths estimated in 2016 (ACS 2016). About 1% of all breast cancers are diagnosed in men (Borgen et al. 1992; Senkus et al. 2015).

The hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer subtype is the most prevalent of breast cancer subtypes and accounts for approximately 70% of all breast cancers (Howlader et al. 2014).

Approximately 90% of patients with breast cancer are diagnosed at an early stage of their disease (Howlader et al. 2016). These patients are treated with curative intent and as such are candidates for local treatments including surgery followed very often by radiotherapy depending on the surgical approach and regional disease extension. After surgery, the indication of adjuvant systemic therapy is based on estimated individual risk of disease relapse and predicted sensitivity to available systemic therapies (that is, estrogen receptor [ER]/progesterone receptor and HER2 status). Most validated clinical and pathological features that may indicate a higher risk of distant disease relapse and therefore the need for adjuvant treatment include large primary tumor size, involvement and degree of involvement of axillary lymph nodes, and high histologic grade.

While gene expression profile of the primary tumor may be used to complement pathology assessment and gain additional prognostic and/or predictive information on the likelihood of disease relapse and chemosensitivity (Senkus et al. 2015), available deoxyribonucleic acid (DNA) microarray technologies are not yet part of routine practice in majority of countries and not globally accessible. Ki-67 antigen (also known as antigen identified by monoclonal antibody Ki-67) is encoded by the MKI67 gene and is a nuclear protein expressed in all phases of the cell cycle other than the G0 phase and has been reported as an independent prognostic factor in early breast cancer (Dowsett et al. 2011). In HR+ breast cancer, patients with high levels of Ki-67 have been shown to have higher disease recurrence rates while receiving adjuvant endocrine therapy following surgery. In the BIG 1-98 study (Viale et al. 2008), patients receiving letrozole with HR+ early breast cancer involving their axillary lymph nodes and low (≤11%) Ki-67 levels at baseline had a 4-year disease-free survival of 93% compared to 85% for patients with higher Ki-67 values (>11%). Currently, there is no consensus as to the precise baseline level of Ki-67 that would differentiate a patient for being of higher or lower risk of disease recurrence whilst on adjuvant endocrine therapy. However, the majority of the panel of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015 was prepared to accept a threshold value of Ki-67 within the range of 20% to 29% (Vasconcelos et al. 2016) as indicative of high-risk group appropriate to receive adjuvant chemotherapy. High-level Ki-67 expression

(that is, ≥20%) by immunohistochemistry (IHC) performed centrally is believed to be a valid factor for high-risk patient selection in Study I3Y-MC-JPCF (JPCF; monarchE).

Patients with lymph node-positive disease are most often candidates for chemotherapy. Standard adjuvant chemotherapy includes anthracycline and/or taxane-based regimen. Adjuvant endocrine therapy is indicated in all patients with detectable ER expression (defined as ≥1% of invasive cancer cells) irrespective of the use of chemotherapy (NCCN Version 2.2016). The choice of endocrine agent (tamoxifen and/or one of the 3 selective aromatase inhibitors: anastrozole, letrozole, or exemestane) is primarily determined by the patient's menopausal status. All aromatase inhibitors have shown similar antitumor efficacy and toxicity profiles in randomized studies in the adjuvant and pre-operative setting. Overall, international clinical guidelines (ESMO - Senkus et al. 2015, Saint Gallen International Expert Consensus - Coates et al. 2015) and NCCN guidelines (NCCN version 2.2016) align on recommendation of adjuvant endocrine therapy for at least 5 years, and for post-menopausal patients, aromatase inhibitors should be at least part of endocrine therapy. In pre-menopausal patients, standard endocrine therapy includes tamoxifen with or without ovarian suppression for 5 to 10 years, or an aromatase inhibitor for 5 years with ovarian suppression in selected patients at high risk of disease recurrence (that is, pretreated with chemotherapy) based on the TEXT and SOFT studies. In postmenopausal patients, use of aromatase inhibitors (both non-steroidal and steroidal) and tamoxifen either sequentially, as monotherapy, or extended therapy for a total duration of 5 to 10 years is a valid option. Men with breast cancer are treated similarly to postmenopausal women, considering testicular suppression with a GnRH analogue.

With current standard of care adjuvant therapy, approximately 30% of women with HR+ breast cancer initially diagnosed with early stage disease experience distant relapse with metastases (Reinert and Barrios 2015). Consequently, there is a critical need for more optimal adjuvant therapy in patients with early HR+ breast cancer who have a high likelihood of distant recurrence.

3.2. Study Rationale

Abemaciclib is an oral, selective, and potent ATP-competitive inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6, respectively). CDK4 and CDK6 promote cell growth by facilitating the progression of cells from the G1 to the S-phase of the mammalian cell cycle. This promotion of cell growth occurs primarily by counteracting the effects of a growth suppressor protein known as the retinoblastoma (Rb) protein, whereby the reversal of Rb-mediated suppression is achieved by the phosphorylation of this protein by CDK4 and/or CDK6. The CDK4/CDK6-Rb pathway is commonly altered in cancer cells, whereby the activation of this pathway contributes to enhanced growth. Accordingly, in cancer cells, abemaciclib inhibits CDK4/CDK6-dependent phosphorylation of Rb, which subsequently blocks proliferation by inhibiting the progression of these cells from the G1 phase into the S and G2/M phases of the cell cycle.

Continuously dosed abemaciclib has demonstrated robust single-agent clinical activity in both the JPBA Phase 1b study with a response rate of 33.3% across dose levels and the I3Y-MC-

JPBN (JPBN; MONARCH 1) Phase 2 study with a response rate of 19.7% (at 200-mg dose twice daily), in patients with heavily pretreated HR+ metastatic breast cancer that is refractory to endocrine therapy (Patnaik et al. 2016; Dickler et al. 2016).

Abemaciclib plus endocrine therapy resulted in statistically significant improvements in both progression-free survival (PFS) and response rate in HR+, HER2− advanced breast cancer in patients who progressed on or following endocrine therapy (I3Y-MC-JPBL [JPBL; MONARCH 2]) and in patients receiving first-line treatment (I3Y-MC-JPBM [JPBM; MONARCH 3]). In MONARCH 2, the median PFS of abemaciclib plus fulvestrant was 16.4 months versus 9.3 months in the control arm with HR=0.553 (95% CI: 0.449, 0.681), p<.0000001 (Sledge et al. 2017). In MONARCH 3, median PFS was not reached in the abemaciclib plus aromatase inhibitor arm and was 14.7 months in the control arm, with an HR of 0.543 (95% CI 0.409 to 0.723, p=.000021 [Di Leo et al. 2017]). Additionally, both studies had significant improvement in ORR. In MONARCH 2 ORR in patients with measurable disease was 48.1% versus 21.3% in the control arm (95% CI: 42.6, 53.6), odds ratio = 3.42, p<.001. In MONARCH 3, ORR in patients with measurable disease was 59.2% versus 43.8% in the control arm (95% CI: 53.3, 65.1), odds ratio = 1.9, p=.004 (Di Leo et al. 2017; Sledge et al. 2017)

In the neoadjuvant breast cancer setting, Study I3Y-MC-JPBY (JPBY; neoMONARCH), a Phase 2 open-label, randomized trial, showed an acceptable safety profile for abemaciclib (150 mg twice daily) as monotherapy and in combination with anastrozole, with reduction of breast cancer tumor cell proliferation marker (Ki-67 index) to a significantly greater extent than anastrozole alone (Hurvitz et al. 2016).

Abemaciclib has an acceptable safety profile in the respective patient populations studied in the 2 Phase 3 trials (MONARCH 2 and MONARCH 3) in combination with endocrine therapy and the Phase 2 study (MONARCH 1), a monotherapy study. The safety monitoring and corresponding dose adjustment guidelines used in these clinical studies effectively improved the tolerability profile of abemaciclib. The most frequently reported adverse events ([AEs], >20%, consistently in these 3 studies) are: diarrhea, neutropenia, fatigue, nausea, vomiting, abdominal pain, decreased appetite, and anemia. Additionally, other clinically relevant AEs are venous thromboembolism (VTE, [including pulmonary embolism (PE) and deep vein thrombosis (DVT)]), ALT increased, AST increased, and interstitial lung disease (ILD)/pneumonitis.

The monarchE study aims to evaluate abemaciclib in combination with standard adjuvant endocrine therapy, in patients with node-positive, early stage, HR+, HER2-, invasive breast cancer at high risk of recurrence as determined by clinical and pathological features. Historical data estimate the 5-year disease-free survival rate for the monarchE-defined population between 80% and 85%. Therefore, at least 15% of the patient population intended to be enrolled into monarchE study fail to be cured by the current standard of care adjuvant therapy. Optimizing standard adjuvant therapy by adding novel targeted therapies is warranted for patients with early breast cancer and at high risk of disease recurrence.

3.2.1. Ki-67 Immunohistochemistry Assay

The investigational Ki-67 pharmDx Kit is manufactured by Dako North America, Inc. This IHC assay will be a Good Manufacturing Practice (GMP) verified assay (the kit protocol and components are locked, manufactured in a GMP facility and analytically verified) and will comply with regional regulatory requirements for investigational devices. Dako's Ki-67 kit is a standardized IHC assay that detects expression of Ki-67 in formalin-fixed paraffin-embedded (FFPE) breast cancer tissue specimens using a Ki-67 Ab that is CE marked.

CCI [redacted]

CCI [redacted]

A key secondary end point is to evaluate all patients from both cohorts who have a Ki-67 index ≥20%. CCI [redacted]

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated serious adverse events of abemaciclib are to be found in the Investigator's Brochure (IB).

More detailed information about the known and expected benefits and risks of standard of care endocrine therapies, such as tamoxifen, anastrozole, letrozole, exemestane, and GnRH agonist, may be found in the respective Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

4. Objectives and Endpoints

Table JPCF.4.1 shows the objectives and endpoints of the study.

Table JPCF.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy, in terms of IDFS, for patients with HR+, HER2- early stage breast cancer for abemaciclib plus adjuvant endocrine therapy versus adjuvant endocrine therapy alone.	IDFS, as defined by the STEEP System (Hudis et al. 2007) (Section 10.3.1.1)
Secondary	
To evaluate the efficacy, in terms of IDFS, for patients with HR+, HER2- early stage breast cancer with pretreatment Ki-67 index ≥20% by central lab	IDFS, as defined by the STEEP System
To evaluate the efficacy of abemaciclib plus adjuvant endocrine therapy versus adjuvant endocrine therapy alone in terms of DRFS and OS	Efficacy endpoints: • DRFS • OS
To assess the safety profile of abemaciclib plus adjuvant endocrine therapy compared to adjuvant endocrine therapy alone	Safety endpoints will include but are not limited to the following: • TEAEs, SAEs, and hospitalizations • Clinical laboratory tests, vital signs, and physical examinations
To evaluate the relationship between abemaciclib, exposure and clinical (efficacy and safety) outcomes	Steady-state trough abemaciclib concentration ($C_{min,ss}$), hazard ratio for IDFS, DRFS, OS, other efficacy and safety endpoints
To evaluate abemaciclib plus adjuvant endocrine therapy, versus adjuvant endocrine therapy alone, in terms of general oncology and breast cancer self-reported health-related quality of life (FACT-B 37-item questionnaire), endocrine therapy-specific symptoms (the FACT-ES 19-item subscale and 2 FACIT-sourced items of cognitive symptoms and 3 FACIT-sourced items for bladder symptoms), and fatigue experienced during abemaciclib and/or endocrine therapy (the FACIT-F 13-item subscale).	Composite and single-item endpoints will be evaluated to examine differentiating effects of abemaciclib across study arms. Measurement will be undertaken using the FACT-B questionnaire for general oncology and breast cancer health-related quality of life; the FACT-ES subscale and additional FACIT-sourced items for cognitive and bladder endocrine therapy symptoms; and the FACIT-F subscale to characterize this symptom know to be associated with oncology, endocrine therapy, and abemaciclib treatment.
To evaluate health status to inform decision modeling for health economic evaluation using the EQ-5D-5L.	The EQ-5D-5L health state profile (the index score and the single-item health status measure) will be used to inform decision modeling for economic evaluations and this questionnaire will be coadministered with and after first completing the FACT/FACIT questionnaire, subscales, and additional items.

Exploratory	
CCI [redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: DRFS = distant relapse-free survival; EQ-5D-5L = EuroQol five-dimension five-level questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy - Fatigue (Version 4); FACIT-sourced items = Functional Assessment of Chronic Illness Therapy Item Library (Version 2) cognitive symptoms items (2) and bladder symptom items (3); FACT-B = Functional Assessment of Cancer Therapy - Breast (Version 4); FACT-ES = Functional Assessment of Cancer Therapy - Endocrine Symptoms (Version 4); HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2-negative; IDFS = invasive disease-free survival; OS = overall survival; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

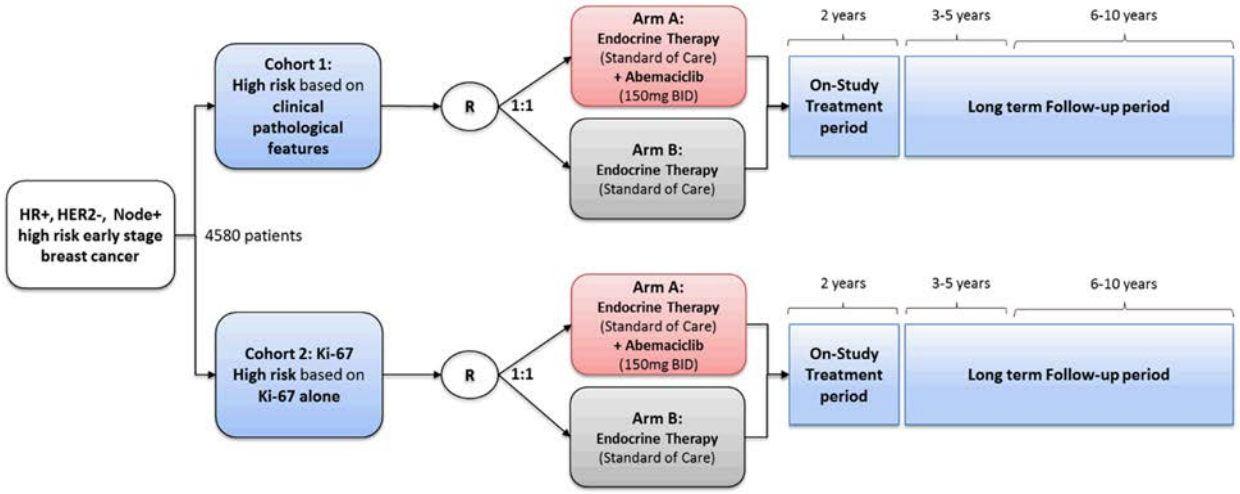
5. Study Design

5.1. Overall Design

The Phase 3 Study monarchE is a multicenter, randomized, open-label trial in patients with node-positive, early-stage, resected HR+, HER2− breast cancer who completed definitive locoregional therapy (with or without neoadjuvant or adjuvant chemotherapy) and are at high risk of disease recurrence. Figure JPCF.5.1 illustrates the study design. Treatment with abemaciclib will be given for up to 2 years or until discontinuation criteria are met, whichever occurs first. Endocrine therapy will be taken as prescribed during the on-study treatment period (Years 1-2). In Year 3 and beyond, standard adjuvant endocrine therapy should continue for a duration of at least 5 years if deemed medically appropriate. In a subset of patients, an investigational assay will be used to determine Ki-67 status.

Standard adjuvant endocrine therapy is per physician's choice (such as tamoxifen or an aromatase inhibitor, with or without ovarian function suppression per standard practice). Adjuvant treatment with fulvestrant is not allowed at any time during the study. Patients currently receiving standard adjuvant endocrine therapy at time of study entry may not have received more than 12 weeks of standard adjuvant endocrine therapy after completion of their last non-endocrine therapy (surgery, chemotherapy, or radiation) prior to randomization. Randomization must occur within a maximum of 16 months following the definitive breast cancer surgery.

In both treatment arms (Arm A: abemaciclib plus endocrine therapy; Arm B: endocrine therapy alone), Day 1 is defined as the first dose of treatment following randomization, that is, abemaciclib and/or endocrine therapy (for Arm A) or endocrine therapy alone (for Arm B), regardless if the patient is already receiving endocrine therapy at time of randomization. The first dose of study treatment (abemaciclib and/or endocrine therapy) should be taken no later than 3 days of randomization.



Abbreviations: BID = twice daily; HER2 = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor-positive; ITT = intent to treat; Ki-67 = prognostic parameter; R = randomization.

Figure JPCF.5.1. Illustration of study design.

5.2. Number of Patients

Patients will be enrolled into 2 cohorts:

1. Cohort 1: those with at least 1 positive node and eligible based on clinical pathological features (degree of axillary lymph node involvement, tumor size, and/or grade) regardless of Ki-67 status.
2. Cohort 2: those with at least 1 positive node and eligible exclusively based on central Ki-67 status. These patients would not be eligible based on degree of axillary lymph node involvement, tumor size, and/or histologic grade.

Approximately 4580 patients will be randomized within cohorts, in a 1:1 ratio to either up to 2 years of abemaciclib plus standard adjuvant endocrine therapy or standard adjuvant endocrine therapy alone.

Note that patients in Cohort 1 may also have high Ki-67, but Ki-67 testing prior to randomization is not required for this cohort.

5.3. End of Study Definition

The primary analysis of the primary endpoint, invasive disease-free survival (IDFS), will be performed after approximately 390 IDFS events have been observed in the Intent-to-Treat (ITT) population. The study will be considered complete (that is, scientific evaluation will be complete [study completion]) following evaluation of overall survival (OS) as determined by Lilly. Investigators will continue to follow the study schedule for all patients until notified by Lilly that

study completion requirement has been met. End of the study is the date of the last visit or last scheduled procedure for the last patient.

5.4. Justification for Dose (Arm A)

In monarchE, abemaciclib will be administered orally at 150 mg twice daily in Arm A, with at least 6-hours separating doses. The minimum separation of 6 hours was selected to approximate the t_{max} of abemaciclib and permit maximal absorption between doses.

Collectively, results from the studies evaluating abemaciclib in the mBC setting (Studies JPBA, JPBH, MONARCH 1, MONARCH 2, and MONARCH 3), and in the early stage breast cancer setting (neoMONARCH), support the abemaciclib dose of 150 mg twice daily. Study JPBA evaluated abemaciclib monotherapy at multiple dose levels in patients with advanced solid tumors. The maximum tolerated dose of single-agent abemaciclib was defined as 200 mg twice daily, with the dose-limiting toxicity of Grade 3 fatigue (Patnaik et al. 2016). The most common AEs experienced by patients receiving abemaciclib included diarrhea and neutropenia, predominantly of low-grade severity.

Based on the safety, tolerability, and PK results from abemaciclib trials in breast cancer referenced above, the selected dose of abemaciclib in ongoing Phase 3 program (MONARCH 2 and MONARCH 3) and further clinical trials for patients with breast cancer is 150 mg twice daily when administered in combination with endocrine therapy. Therefore, in monarchE Arm A, up to 2 years of abemaciclib will be administered orally at 150 mg twice daily (with minimum of 6-hour interval separating doses) in combination with standard adjuvant endocrine therapy of physician's choice.

6. Study Population

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

6.1. Inclusion Criteria

A patient is eligible to be included in the study only if she/he meets all of the following criteria:

[1] Female (regardless of menopausal status) or male ≥18 years of age (or of an acceptable age according to local regulations, whichever is older).

[2] The patient has confirmed HR+, HER2-negative (HER2-), early stage resected invasive breast cancer without evidence of distant metastases.

- To fulfill the requirement for HR+ disease by local testing on primary disease specimen, tumor must be ER or PgR positive defined by immunohistochemistry (IHC) according to American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for hormone receptor testing (Hammond et al. 2010).
- To fulfill the requirement of HER2- disease by local testing on primary disease specimen, tumor must be HER2- according to ASCO/CAP guidelines for HER2 testing (Wolff et al. 2018).

Patients with bilateral breast cancer (diagnosis of invasive tumors in both breasts simultaneously or within 6 months of each other) can be eligible if all lesions tested on both sides are HR+/HER2- and adequate surgery has been performed in both breasts (see inclusion criterion [3]). The Lilly Clinical Research Physician and Clinical Research Scientist (CRP/CRS) must be consulted for all cases of bilateral breast cancer.

[3] The patient must have undergone definitive surgery of the primary breast tumor(s).

- With the exception of the situations described below, the margins of the resected specimen must be histologically free of invasive tumor and /or a component of ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional excisions may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo mastectomy to be eligible. Of note, patients with margins positive for lobular carcinoma in situ (LCIS) are eligible without additional resection.

- For patients who undergo mastectomy or wide local excision where deep margin abuts the pectoralis fascia, patients with microscopic positive margins are eligible as long as radiotherapy of the chest wall is administered prior to study entry. Patients with positive anterior margins may be eligible if there is no gross disease left behind (radiotherapy as per local guidelines).
- Where surgical excision of supraclavicular or internal mammary nodes is not feasible, residual nodes should be irradiated in accordance with standard guidelines.
- If given, radiation therapy (for example, post-mastectomy or post-lumpectomy) should be administered according to standard guidelines.

[4] The patient must have tumor tissue from breast (preferred) or lymph node for exploratory biomarker analysis available prior to randomization.

Note: Sites should confirm the availability of tumor tissue for exploratory analysis (Section 9.8.2.2) with the pathological laboratory prior to randomization

[5] Patients must be node positive (microscopic and macroscopic tumor involvement are allowed; ipsilateral internal mammary and supraclavicular lymph nodes are allowed, but will not count toward the number of positive lymph nodes) and fulfill one of the following criteria:

A. Pathological tumor involvement in ≥4 ipsilateral axillary lymph nodes.

OR

B. Pathological tumor involvement in 1 to 3 ipsilateral axillary lymph node(s) (for patients who received neoadjuvant therapy also cytological tumor involvement at time of initial diagnosis is allowed) and meet at least 1 of the following criteria:

1. Grade 3 as defined by a combined score of at least 8 points per the modified Bloom-Richardson grading system (Elston and Ellis 1991), also known as the Nottingham scale, or equivalent following discussion with the Lilly CRP/CRS

– pathological primary invasive tumor size ≥5 cm (for patients who received neoadjuvant therapy primary tumor size ≥5 cm on breast imaging is allowed). Note: if tumor size is needed to meet eligibility criteria, patients with multifocal/multicentric tumors may be eligible based on the addition of diameters of the individual lesions following discussion with the Lilly CRP/CRS.

– Ki-67 index of ≥20% (for Cohort 2) on untreated breast tissue as determined by the investigational assay (described in Section 3.2.1) at the Study JPCF central laboratory. See Section 9.8.1 for Ki-67 sample requirements.

[6] The patient must be randomized within 16 months from the time of definitive breast cancer surgery.

[7] If the patient is currently receiving or initiating standard adjuvant endocrine therapy at time of study entry, she/he may receive up to 12 weeks of endocrine therapy until randomization following the last non-endocrine therapy (surgery, chemotherapy, or radiation), whichever is last.

Use of GNRH analogues for ovarian suppression is not considered endocrine therapy for the purposes of this criterion. Note: Adjuvant treatment with fulvestrant is not allowed.

[8] Patients who received or will be receiving adjuvant chemotherapy must have completed adjuvant chemotherapy prior to randomization and patients must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to randomization. Patients who are not candidates for adjuvant chemotherapy or decline chemotherapy are permitted. Patients may also have received neoadjuvant chemotherapy. A washout period of at least 21 days is required between last adjuvant chemotherapy dose and randomization (provided the patient did not receive radiotherapy).

[9] Patients who received or will be receiving adjuvant radiotherapy must have completed radiotherapy prior to randomization, and patients must have recovered (Grade ≤1) from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and randomization.

[10] The patient has recovered from surgical side effects following definitive breast surgery based on investigator discretion (for example, adequate wound healing complications or seroma complications).

[11] Omit text; see Criterion [1]

[12] Women of reproductive potential must have a negative blood pregnancy test at baseline (within 14 days prior to randomization) and agree to use highly effective contraceptive methods to prevent pregnancy during the study and for 12 weeks following the last dose of study treatment. Males must agree to use an acceptable method of birth control and to not donate sperm during the study and for at least 12 weeks following the last dose of study treatment.

Refer to Appendix 4 for definitions of highly effective methods of contraception.

[13] The patient has a performance status ≤1 on the Eastern Cooperative Oncology Group (Appendix 11) scale (Oken et al. 1982).

[14] The patient has adequate organ function for all of the following criteria, as defined below.

System	Laboratory Value
Hematologic	
ANC	≥1.5 × 10^9/L Note: G-CSF cannot be administered to meet ANC eligibility criterion.
Platelets	≥100 × 10^9/L
Hemoglobin	≥8 g/dL Note: Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin earlier than the day after the erythrocyte transfusion.
Hepatic	
Total bilirubin	≤1.5 × ULN Patients with Gilbert's syndrome with a total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are permitted.
ALT and AST	≤3 × ULN

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; G-CSF = granulocyte colony-stimulating factor; ULN = upper limit of normal.

[15] The patient is able to swallow oral medications.

[16] The patient has given written informed consent prior to any study-specific procedures and is willing and able to make herself/himself available for the duration of the study and amenable and able to follow study schedule during treatment and follow-up.

6.2. Exclusion Criteria

A patient will be excluded from the study if she/he meets **any** of the following criteria:

[17] The patient has metastatic disease (including contralateral axillary lymph nodes) or lymph node-negative breast cancer. Patients with inflammatory breast cancer are excluded. Inflammatory carcinoma should not apply to a patient with neglected locally advanced breast cancer presenting late in the course of their disease (American Joint Committee on Cancer [AJCC] staging system for breast cancer 8th edition, Hortobagyi et al. 2017). The investigator should consult with the Lilly CRP/CRS regarding eligibility of patients with neglected inflammatoid disease.

[18] Patients with a history of previous breast cancer are excluded, with the exception of ipsilateral DCIS treated by locoregional therapy alone ≥5 years ago. Patients with a history of contralateral DCIS treated by local regional therapy at any time may be eligible. Patients with a history of any other cancer (except non-melanoma skin cancer or carcinoma in situ of the cervix), unless in complete remission with no therapy for a minimum of 5 years from the date of randomization are excluded. For patients with a history of other non-breast cancers within 5 years from the date of randomization and considered of very low risk of recurrence per investigator's judgment (for example, papillary thyroid cancer treated with surgery), eligibility is to be discussed with the Lilly CRP/CRS.

[19] Females who are pregnant or lactating.

[20] The patient has previously received treatment with any CDK4 and CDK6 inhibitor.

[21] The patient is receiving concurrent exogenous reproductive hormone therapy (for example, birth control pills, hormone replacement therapy, or megestrol acetate). Appropriate washout period between last dose of exogenous hormone therapy and randomization is up to the investigator's medical judgment (for example, applying 5 times the half-life elimination rule). Note: topical vaginal estrogen therapy is permitted if all other non-hormonal options are exhausted.

[22] The patient has previously received endocrine therapy for breast cancer prevention (tamoxifen or aromatase inhibitors) or raloxifene.

[23] The patient has serious preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (such as severe renal impairment, *[for example, estimated creatinine clearance <30 mL/min],* interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in clinically significant diarrhea).

[24] The patient has a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Exception: patients with controlled atrial fibrillation for >30 days prior to randomization are eligible. Any patient with a history of VTE (for example, DVT of the leg or arm and/or PE) will be excluded. Patients with a history of venous catheter occlusion by thrombus that did NOT surround the catheter, and the lumen could be made patent by appropriate measures (for example, saline or thrombolytic agent), are not excluded.

[25] The patient has active systemic infections (for example, bacterial infection requiring intravenous [IV] antibiotics at time of initiating study treatment, fungal infection, or detectable viral infection requiring systemic therapy) or viral load (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]). Screening is not required for enrollment.

[26] The patient has had major surgery within 14 days prior to randomization.

[27] The patient has received an experimental treatment in a clinical trial within the last 30 days or 5 half-lives, whichever is longer, prior to randomization, or is currently enrolled in any other type of medical research (for example: medical device) judged by the sponsor not to be scientifically or medically compatible with this study. Co-enrollment to other studies may be allowed following consultation with the Lilly CRP/CRS.

6.3. Lifestyle Restrictions

Patients should avoid consumption of grapefruit or grapefruit juice while receiving abemaciclib. Patients should not donate blood during the on-study treatment period and for 3 months after discontinuing study treatment. See Section 7.7 for additional guidance on concomitant therapy to avoid whenever possible.

6.4. Screen Failures

A patient who fails screening is allowed to screen again after signing a new informed consent form (ICF) and will be assigned a new patient number under the conditions specified in this section.

The Ki-67 expression result obtained under the first patient number can be moved to a new number in an effort to preserve patient tissue. A patient may not be rescreened in an effort to obtain a different Ki-67 result.

Repeating of laboratory tests during the 3-month screening period does not constitute re-screening. This includes one repeat for Ki-67 to determine Cohort 2 eligibility if Ki-67 expression was not able to be determined by the patient's initial sample.

The following patients may be eligible for rescreening in any of the following circumstances:

- A patient who has become eligible to enroll in the study as the result of a protocol amendment.
- Patient status has changed such that the eligibility criterion that caused the patient to screen fail would no longer cause the patient to screen fail again.
- A patient who completes screening and meets all inclusion and exclusion requirements but is unable to be enrolled due to extenuating circumstances (such as severe weather, death in family, child illness).

The investigator should contact the Lilly study team prior to rescreening a patient.

7. Treatments

7.1. Treatments Administration

Patients will be randomized to one of the following treatment arms:

- Arm A - Abemaciclib plus standard adjuvant endocrine therapy
- Arm B - Standard adjuvant endocrine therapy alone

The monarchE protocol defines study treatment as abemaciclib and/or endocrine therapy during the first 2 years of the on-study treatment period.

In both arms A and B, Day 1 of on-study treatment period is defined by the first dose of treatment following randomization, which means abemaciclib and/or endocrine therapy (in Arm A) or endocrine therapy (in Arm B), regardless if the patient is already receiving endocrine therapy prior to randomization. The first dose of abemaciclib and/or endocrine therapy should be taken no later than 3 days after randomization.

The on-study treatment period ends after one of the following time points, whichever occurs first:

- after the completion of the 2-year on-study treatment period
- after discontinuation criteria are met (Section 8.1) and patient has discontinued all study treatment (abemaciclib plus endocrine therapy in arm A, endocrine therapy in Arm B) prior to the completion of the 2-year on-study treatment period

Table JPCF.7.1 shows the treatment regimens.

Table JPCF.7.1. Treatment Regimens

	Dose and Schedule		
Arm	**Abemaciclib**	**Standard Adjuvant Endocrine Therapy**	**On Study Treatment Period (Years 1-2)**
A	150 mg twice daily, with at least 6-hour separating doses	Standard adjuvant endocrine therapy of physician's choice	Treatment with abemaciclib will be given for up to 2 years or until discontinuation criteria are met. In both arms, treatment with endocrine therapy will be given until discontinuation criteria are met[a]
B	Not applicable	Standard adjuvant endocrine therapy of physician's choice	

[a] Standard endocrine therapy will be taken as prescribed during the on-study treatment period (Years 1-2). In Year 3 and beyond, continue standard adjuvant endocrine therapy to complete at least 5 years, if this is medically appropriate.

7.1.1. Treatment Administration Guidance:

Abemaciclib (Arm A):

Abemaciclib will be administered at a starting dose of 150 mg twice daily and it is provided as 50-mg capsules or tablets. Abemaciclib should be taken twice daily (with at least 6-hour separating doses) at the same time each day with a glass of water. Patients should be instructed to swallow capsules or tablets whole and not open, chew, or crush.

Endocrine therapy (Arms A and B):

The investigator should refer to the product label for administration of standard-of-care endocrine therapy of choice. A switch to another standard endocrine therapy is allowed as per the investigator's discretion only in the absence of an IDFS event (Appendix 10), during the on-study treatment period. Adjuvant treatment with fulvestrant is not allowed at any time during the study.

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/study site personnel,
- verifying that instructions are followed properly by the patient,
- maintaining accurate records of abemaciclib dispensing and collection as well as for other treatments provided locally by Lilly. For all other treatments, follow local regulations,
- at the end of the study returning all unused treatments provided by Lilly, including abemaciclib and locally provided other treatments, (not site sourced, see Section 7.1.2) to sites for destruction if the site has been approved for destruction. Sites not approved for destruction of treatments should return materials to Lilly, or its designee.

7.1.2. Packaging and Labeling

Abemaciclib will be provided by Lilly. Clinical trial materials will be labeled according to the country's regulatory requirements. All standard adjuvant endocrine therapy per physician's choice (such as letrozole, anastrozole, exemestane, tamoxifen, or GnRH agonist) will be site sourced unless prohibited by local country regulation.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomly assigned to Arm A or Arm B. Approximately 4580 patients, will be enrolled and randomized 1:1 between the 2 arms.

Randomization will occur within cohort and will be stratified by the factors outlined in Section 10.1.

The interactive web-response system (IWRS) will use randomization factors to assign treatment arm to each patient.

The IWRS will be used to assign bottles containing open-label abemaciclib to each patient in Arm A.

7.2.1. Selection and Timing of Doses

During the on-study treatment period, a delay of study treatment due to holiday, weekend, inclement weather, or other unforeseen circumstances will be permitted for a maximum of 7 consecutive days and not counted as a protocol deviation. In exceptional cases, for planned delays (including but not limited to vacation or holidays), additional study treatment may be dispensed. In these cases, patients should return to the original visit schedule calculated from the last (clinic) visit within the visit window.

In Arm A, abemaciclib will be administered orally at 150 mg twice daily, with at least 6-hour separating doses on a continuous schedule. Details on treatment administration are described in Section 7.1. Treatment with abemaciclib will be given for up to 2 years or until discontinuation criteria are met (see Section 8).

Standard adjuvant endocrine therapy will be taken as prescribed during the on-study treatment period (Years 1-2). In Year 3 and beyond, standard endocrine therapy may be continued to complete at least 5 years according to standard of care and if deemed medically appropriate based on investigator discretion. A switch to another standard endocrine therapy is allowed as per the investigator's discretion and in the absence of an IDFS event per STEEP criteria (Appendix 10), during the on-study treatment period.

In Arm A, timing of endocrine therapy administration relative to abemaciclib is up to the investigator.

7.3. Blinding

This is a randomized, open-label study. Toxicities and laboratory abnormalities related to abemaciclib treatment (such as diarrhea, neutropenia, and creatinine increase) have the potential to unblind the study, justifying an open-label design. Randomization will occur using an IWRS. Assignment to treatment groups will be determined by a computer-generated random sequence. Each patient in this study will be aware of his or her own assigned treatment group. At each investigative site, all staff involved in treating and caring for study patients will have full knowledge of treatment assignments for the patients under their care.

In order to maintain the scientific integrity of this trial, access to study data will be strictly controlled prior to the interim and final analyses. Access to the electronic data capture (eDC) system will be limited to those who require this information for their role and all access will be documented.

For the accumulated aggregate database, that is, the database to which Lilly statisticians (or those of its designee) have access, treatment assignment and other parameters that can disclose treatment assignment will be scrambled or masked. Therefore, the sponsor and all investigative sites will remain blinded to treatment group assignments for the aggregate database until the database lock for the final analysis. Scrambled treatment assignments will be used in the

reporting database until the study reaches its final analysis or the study is determined to be positive by the data monitoring committee (DMC). During this time, analyses using unblinded treatment codes will be performed only at the interim analysis points specified in the protocol/statistical analysis plan (SAP).

For those safety and efficacy analyses assigned to the DMC, only the designated Statistical Analysis Center (SAC), which is independent of the sponsor, will perform analyses on unblinded data, that is, an aggregate database with correct treatment assignments. At the request of the sponsor, the SAC may provide pooled summary reports of the data to the sponsor (for example, a summary of AEs across the study). These reports will not include treatment arms.

Further details are included in the study blinding plan.

7.4. Abemaciclib Dosage Modification

7.4.1. Abemaciclib Dose Adjustments

Table JPCF.7.2 is a guidance for management of treatment-emergent, related, and clinically significant AEs of abemaciclib. If an investigator would like to suspend or reduce doses without one of the criteria below being met, this is acceptable and would not be considered a protocol deviation.

Guidance on safety monitoring for hepatic function, renal function, and VTEs is outlined in Section 9.4.

Table JPCF.7.2. Abemaciclib Dose Adjustments for Treatment-Emergent, Related,* and Clinically Significant Adverse Events

Treatment-emergent laboratory abnormalities of neutrophil count decreased and/or ALT/AST increased, regardless of clinical significance, must follow the dose adjustment table below. For VTEs see monitoring and guidance in Section 9.4.4 and Appendix 12.

* Related means there is a reasonable causal relationship with abemaciclib.

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose reduction is NOT required.
Hematologic Toxicity	Recurrent[a] Grade 3 or Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic Toxicity: **If patient requires administration of blood cell growth factors**	Regardless of severity (Use of growth factors according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level unless already performed for incidence of toxicity that led to the use of growth factor.
Non-hematologic Toxicity[b] (except diarrhea, ALT/AST increased, ILD/pneumonitis and VTE[d])	Persistent or recurrent[a] Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1, or Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea	Grade 2 that does not resolve within 24 hours to at least Grade 1	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose reduction is NOT required.
Diarrhea	Persistent or recurrent[a] Grade 2 that does not resolve with maximal supportive measures, or requires hospitalization, or Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT/AST Increased	Persistent or recurrent[a] Grade 2 (>3.0-5.0×ULN), or Grade 3 (>5.0-20.0×ULN)[c]	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT/AST Increased	Grade 4 (>20.0×ULN)	Abemaciclib therapy **MUST** be discontinued.	Abemaciclib therapy **MUST** be discontinued.
ALT/AST Increased	Elevation in AST and/or ALT >3 x ULN with total bilirubin >2 x ULN, in the absence of cholestasis	Abemaciclib therapy MUST be discontinued	Abemaciclib therapy MUST be discontinued.
ILD/pneumonitis	Grade 2	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.

ILD/pneumonitis	Grade 3 or Grade 4	Abemaciclib therapy MUST be discontinued	Abemaciclib therapy MUST be discontinued.

Abbreviations: ALT = alanine transaminase; ASCO = American Society of Clinical Oncology; ILD = interstitial lung disease.

[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:

The patient showed stable hematological counts (Grade ≤2) during that timeframe
In the absence of any infectious sign or risk factor
The patient is benefiting from study treatment

[b] Additional guidance for renal and hepatic monitoring is in Section 9.4.

[c] Grade 3 ALT/AST increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 9.4 for additional guidance for hepatic monitoring.

[d] For VTE, dose reduction of abemaciclib will be at the discretion of the investigator.

7.4.1.1. Dose Adjustments

7.4.1.1.1. Abemaciclib (Arm A)

Dose adjustments as outlined in Table JPCF.7.3 are allowed. Abemaciclib should be reduced sequentially by 1 dose level.

For patients requiring dose reduction(s), any re-escalation to a prior dose level is permitted only after consultation with the Lilly CRP/CRS. After re-escalation, subsequent dose adjustments should be based on the dose of abemaciclib that the patient is currently receiving.

Table JPCF.7.3. Dose Adjustments of Abemaciclib

Dose Adjustment	Oral Dose	Frequency
0	150 mg	Twice daily with at least 6 hours between doses
1	100 mg	Twice daily with at least 6 hours between doses
2	50 mg	Twice daily with at least 6 hours between doses

If a patient receiving the 50-mg twice daily dose of abemaciclib requires further dose reduction, the patient must be discontinued from abemaciclib.

Patients undergoing surgery:

- For minor surgeries and procedures (for example, ambulatory), investigators should treat as clinically indicated and closely monitor any signs of infection or healing complications.
- For major surgeries, the recommendation is to suspend dosing of abemaciclib for at least 7 days before and may be resumed as clinically indicated.
- Consider monitoring neutrophils and platelets before surgery and before resuming abemaciclib. The scars should be aseptic and healing process be reasonable before resuming abemaciclib.

- Dose suspensions ≥28 days must be discussed with Lilly CRP/CRS.

7.4.1.1.2. Standard of Care Endocrine Therapy of Physician's Choice (Arms A and B)

Dose adjustment for endocrine therapy (on-study treatment period and beyond) will be determined by the investigator and when applicable. For Arm A, in the event that endocrine therapy is permanently discontinued for any reason other than an IDFS event per STEEP criteria (Appendix 10), a patient should continue to receive abemaciclib. A switch to another endocrine therapy is permitted per physician's choice as part of standard of care. In the event that abemaciclib must be discontinued, a patient may continue to receive endocrine therapy per the investigator's clinical judgment.

For patients in Arm B undergoing surgery, a determination regarding changes to endocrine therapy is as clinically indicated and determined by the investigator.

7.4.1.2. Dose Delays and Omission

7.4.1.2.1. Study Treatment (Abemaciclib and/or Endocrine Therapy – Arms A and B)

Both dose suspension and delay of study treatment are permitted. When a dose suspension or delay occurs related to toxicity (defined as an AE possibly related to study treatment per investigator judgment), the relevant drug (abemaciclib and/or endocrine therapy) may be suspended or delayed as determined by the investigator's judgment and the other drug may be continued (see Table JPCF.7.2 for guidance on abemaciclib toxicity management).

Study treatment may be held up to 28 days to permit sufficient time for recovery from the toxicity. For patients not recovering from toxicity within 28 days, a delay >28 days is permitted upon agreement between the investigator and the Lilly CRP/CRS and abemaciclib dose adjustment is to be considered.

In the event of a study visit 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 the patient not having sufficient drug supply, study treatment may be delayed up to 7 days (and not be considered a protocol violation). In exceptional circumstances, a delay >7 days is permitted upon agreement between the investigator and the Lilly CRP/CRS. Early distribution of study treatment is also permitted in certain circumstances (for example, planned vacation).

7.5. Preparation/Handling/Storage/Accountability

For Arm A, abemaciclib will be supplied by Lilly as capsules or tablets for oral administration. Abemaciclib capsules or tablets should be stored according to the temperature range listed on the product label, and should not be opened, crushed, or chewed. Patients should store the abemaciclib capsules or tablets in the original package provided and be instructed to keep all medication out of reach of children.

7.6. Treatment Compliance

Patient compliance with abemaciclib will be assessed by reconciliation at qualified visits. Study medication administration data will be recorded in the patient's medical record and case report form (CRF).

Patients who are significantly noncompliant with abemaciclib may be discontinued from abemaciclib treatment. A patient will be considered significantly noncompliant if she or he repeatedly misses more than 25% of abemaciclib doses between scheduled clinic visits. Similarly, a patient will be considered significantly noncompliant if she or he is judged by the investigator to have intentionally or repeatedly taken more than (≥125%) the prescribed amount of medication. Abemaciclib dose suspensions or delays related to toxicity may occur and will not result in a patient being considered as noncompliant.

Patient compliance to standard endocrine therapy will be collected and recorded in the patient's medical record and CRF. During the on-study treatment period (Y1-2), this comprises information on dosing, treatment omissions, changes in endocrine therapy, and treatment discontinuation. During the long-term follow-up period, information on changes in endocrine therapy and treatment discontinuation will be recorded (refer to Section 2; Schedule of Activities).

7.7. Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, concomitant medications, and supplements must be captured at each visit in the CRF. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the short-term follow-up visit.

In general, the list of prohibited medications that affect patient eligibility or participation in the study are limited to endocrine therapy for breast cancer prevention, concurrent exogenous reproductive hormone therapy, and recent experimental treatment in a clinical trial. Further details of these prohibited medications are provided in the exclusion criteria in Section 6.2.

There are a number of concomitant medications that should be substituted or avoided if possible, but do not affect patient eligibility or participation in the study. It should be noted that for patients assigned to receive abemaciclib, investigators should consult with their local pharmacist to evaluate any potential concerns combining a concomitant medication with abemaciclib. Further details of the medications that should be substituted or avoided if possible are provided below and in Appendix 8.

Concurrent treatment with standard of care bone-modifying agents (such as bisphosphonates and denosumab) is permitted. With the exception of standard endocrine therapy for breast cancer, no other anticancer therapy will be permitted while patients are on study treatment unless previously discussed with the Lilly CRP/CRS. Of note, megestrol acetate and fulvestrant are not permitted.

Abemaciclib is extensively metabolized through oxidation by CYP3A. In clinical drug interaction studies, coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure (AUC) to abemaciclib by 3.4-fold (Study I3Y-MC-JPBE) and coadministration of

rifampin, a strong CYP3A inducer, decreased exposure to abemaciclib by 95% (Study I3Y-MC-JPBF). Therefore, grapefruit or grapefruit juice as well as inducers and inhibitors of CYP3A should be substituted or avoided if possible (Appendix 8).

Abemaciclib can be coadministered with drugs which are substrates of CYP enzymes.

Abemaciclib and/or its major metabolites inhibit the efflux transporters P-glycoprotein and breast cancer resistance protein and renal transporters organic cation transporter 2, multidrug and toxin extrusion protein 1 (MATE1) and MATE2-K at clinically relevant concentrations. Therefore, substrates of these transporters such as metformin and those with a narrow therapeutic index such as digoxin and dofetilide should be substituted or avoided if possible.

In the LTFU period, post-discontinuation therapies for the disease under study will be captured along with any regimen changes and start and stop dates for endocrine therapy.

7.7.1. Supportive Care

Patients should receive full supportive care to maximize quality of life (for example, antiemetics or standard of care bone-modifying agents) based on the judgment of the treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP/CRS. Use of any supportive care therapy should be reported on the CRF.

Guidelines regarding the use of other specific supportive care agents are presented below.

7.7.1.1. Supportive Management for Diarrhea (Arm A)

At randomization, patients in Arm A should receive instructions on the management of diarrhea. Patients should be prescribed antidiarrheal therapy (for example, loperamide) on Visit 1. Sponsor will provide reimbursement for antidiarrheal therapy according to local laws.

In the event of diarrhea, provided antidiarrheal therapy should be initiated as early as possible and site should follow the guidance below:

- At the first sign of loose stools, the patient should initiate antidiarrheal therapy, if not already receiving such therapy (for example, loperamide), and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with antidiarrheal therapy within 24 hours to either baseline or Grade 1, study drug should be suspended until diarrhea is resolved to baseline or Grade 1.
- When abemaciclib recommences, dosing should be adjusted as outlined in Table JPCF.7.2 and Section 7.4.1.1.1.

In cases of significant diarrhea, Grade 2 through 4 (Appendix 9), which has not responded to interventions as outlined above, if the investigators are considering the addition of steroids to treat potential colitis, the sponsor strongly recommends an endoscopic procedure to document colitis prior to initiating steroids.

In severe cases of diarrhea, the measuring of neutrophil counts and body temperature 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 IV fluid (IV hydration) and electrolyte replacement.

7.7.1.2. Therapy for Febrile Neutropenia

Patients experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of IV antibiotic therapy. Events that require a patient to be hospitalized are considered SAEs (see Section 9.2.1).

7.7.1.3. Growth Factor Therapy

Growth factors cannot be administered to a patient to satisfy study inclusion criteria.

Growth factors may be administered in accordance with ASCO guidelines (Smith et al. 2015). Dosing of abemaciclib must be suspended if the administration of growth factors is required and must not be recommenced within 48 hours of the last dose of growth factors having been administered. Following the administration of growth factors, the dose of abemaciclib must be reduced by 1 dose level on recommencement, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

7.8. Treatment after the End of the Study

Investigators will continue to follow Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred. Study completion will occur following the final analysis of OS, as determined by Lilly.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Patients will be discontinued from study treatment (abemaciclib plus endocrine therapy combination in Arm A; endocrine therapy in Arm B) in the following circumstances:

- the patient is enrolled in any other clinical trial involving an investigational product or 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 treatment
  - 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 drug occurs prior to introduction of the new agent
- patient decision
  - the patient requests to be withdrawn from the study or study treatment
- 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 patient becomes pregnant during the study; see Section 9.2 regarding regulatory reporting requirements on fetal outcome and breastfeeding
- the patient is significantly noncompliant with study procedures and/or treatment
- the patient experiences any of the IDFS events as per STEEP criteria (Appendix 10)
- unacceptable toxicity

Patients who are discontinued from abemaciclib plus endocrine therapy combination in Arm A or endocrine therapy in Arm B will remain in the study and have short-term follow-up visit and long-term follow-up procedures performed as shown in the Schedule of Activities (Table JPCF.2.1).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If Lilly or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a decision on whether or not the patient may remain on treatment will be made between the Lilly CRP/CRS and the investigator. If both agree that it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without study treatment.

8.2. Discontinuation from the Study

Patients will be discontinued from the study in the following circumstances:

- sponsor determines that participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- the investigator decides that the patient should be discontinued from the study
- the patient requests to be withdrawn from the study
- the study has been completed as defined in Section 5.3.

If a patient decides at any point during the trial that they do not wish to continue with the full study schedule of assessments but are still willing to provide important study information (for example, disease recurrence information and/or survival status information) then the patient should continue in the study and information should continue to be collected in the clinical database. However, if a patient does not wish to have any further data collected, only then should they be considered as withdrawing consent from the study. To minimize such cases of early withdrawal, the investigator should discuss the options with the patient. If the patient is willing to provide information on the important study endpoints (disease recurrence and OS), she/he would remain in the study.

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Study site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow-up.

Study site personnel, or an independent third party, will attempt to collect the survival status for all randomized patients who are lost to follow-up, including randomized patients who do not receive study treatment, within legal and ethical boundaries. Public sources may be searched for survival status information if allowed by local regulations. If the patient's survival status is determined, the survival status will be documented, and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect survival status information.

9. Study Assessments and Procedures

Section 2 provides the Schedule of Activities for this study.

Appendix 3 provides a list of the laboratory tests that will be performed for this study.

Appendix 6 provides the schedule for collection of samples in this study.

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days after receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

9.1.1. Routine Systemic Imaging

For details, see Schedule of Activities (Section 2).

All applicable imaging will be done locally. No central imaging assessments will be performed during the study. See the schedule of activities (Table JPCF.2.1) for detailed description of imaging and collection of disease recurrence information.

During screening, at a minimum, an initial diagnostic/staging work-up since diagnosis is required prior to randomization. The appropriate imaging methods are per the investigator judgment.

During treatment and follow-up, imaging is to be performed per the investigator's judgment and according to routine standard practice. Importantly, for the purpose of disease recurrence documentation, Appendix 10 provides guidance for most appropriate methods, including where cytological and/or histopathological evidence of progression is required.

Detection of symptoms suspicious of disease recurrence is highly important. The investigator, or another medically qualified individual, is expected to conduct a comprehensive and systematic assessment of these symptoms during clinic and phone visits. Of note, the protocol does not prohibit more frequent monitoring by imaging, if judged necessary by the investigator.

The primary endpoint of this study is IDFS as defined by the STEEP System (Hudis et al. 2007). Invasive disease-free survival time is measured from the date of randomization to the date of first occurrence of:

- ipsilateral invasive breast tumor recurrence
- regional invasive breast cancer recurrence
- distant recurrence
- death attributable to any cause
- contralateral invasive breast cancer
- second primary non-breast invasive cancer

Patients for whom no event has been observed will be censored on the day of their last assessment for recurrence or date of randomization if no post-baseline clinic visit occurred.

Distant relapse-free survival (DRFS), a secondary endpoint, is defined as the time from randomization to distant recurrence or death from any cause, whichever occurs first. For patients who experienced an IDFS event other than distant recurrence or death, assessments will continue to be performed until an event of distant recurrence, death, or study completion, whichever occurs first.

Assessments will also be performed for patients who discontinue treatment without an IDFS event per STEEP criteria (Appendix 10) or who are randomized and never received study treatment.

See Section 10.3.1 for complete definitions of the efficacy endpoints.

9.1.2. Appropriateness of Assessments

The measures used to assess safety and efficacy in this study are consistent with those used in most conventional oncology adjuvant trials.

See Appendix 10 for details on breast cancer recurrence and other cancer events. Documentation of a breast cancer recurrence requires meeting at least one of the criteria defined in Appendix 10. Suspicious findings do not provide adequate documentation of a breast cancer recurrence and should not be an indication to alter study treatment. Tumor marker evaluations alone do not document breast cancer recurrence.

9.2. Adverse Events

The investigator will enter verbatim terms and assign toxicity grades according to CTCAE Version 4.0 (NCI 2009).

Investigators are responsible for:

- monitoring the safety of patients in this study and for alerting Lilly or its designee to any AE that seems unusual, even if this AE may be considered an unanticipated benefit to the patient
- the appropriate medical care of patients during the study,
- documenting their review of each laboratory safety report
- following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to study treatment or the study, or that caused the patient to discontinue study treatment before completing the study. The patient should be followed until the AE resolves, is no longer considered to be drug- or procedure-related, becomes stable or returns to baseline, the patient starts a new therapy, the patient dies or becomes lost to follow-up. Frequency of follow-up evaluation is left to the discretion of the investigator.

Abnormal laboratory values should ONLY be reported as an AE if they are clinically relevant.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

Adverse events will be collected after the main ICF is signed starting 28 days prior to randomization. Adverse events for screen failures should only be collected if they are related to study procedures or are the reason for screen failure. All events that occur between signing ICF and 28 days prior to randomization should be captured in the medical history form. In addition, study site personnel will record via CRF any change in the preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study procedure or study treatment via CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatments, or other pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the study treatment and/or study procedure and the AE.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must report any dose modifications or treatment discontinuations that result from AEs to Lilly or its designee via CRF, clarifying, if possible, the circumstances leading to the dose modification or discontinuation of treatment.

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.

Although all AEs after signing the ICF and within 28 days of randomization are recorded in the CRF, SAE reporting begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must notify Lilly or its designee of any SAE within 24 hours of investigator awareness of the SAE via a Lilly-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.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE but should be reported. However, to fulfill regulatory requirements, any pregnancy

should be reported following the SAE process to collect data on the outcome for both mother and fetus.

All SAEs must be collected for 5 years, regardless of causality, relatedness, or the arm to which the patient was initially randomized. Following the 5 years, if the investigator learns of any SAE, including death, at any time, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Investigators are not obligated to actively seek AEs in patients once they have discontinued and/or completed the study (the patient summary CRF has been completed).

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

Serious adverse events, including death, caused by disease recurrence should not be reported unless the investigator deems them to be possibly related to study treatment.

9.2.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are not listed in the IB and that the investigator identifies as related to study treatment or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance 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 guidance.

9.2.3. Complaint Handling

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

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

There is no known antidote to abemaciclib overdose. In case of overdose, the patient should receive supportive measures. Refer to the Product Labels for each of the standard endocrine therapy of physician's choice.

9.4. Safety

Safety will be monitored by an independent DMC, as described in Section 7.3. Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

9.4.1. Other Safety Measures

For each patient, vital signs, laboratory tests, or other tests should be collected as shown in the Schedule of Activities (Section 2).

Any clinically significant findings that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via CRF.

Additional information regarding guidance for monitoring hepatic function, renal function, VTE, and ILD/pneumonitis can be found in Sections 9.4.2, 9.4.3, 9.4.4, and 9.4.5.

9.4.2. Safety Monitoring: Hepatic Function (Both Arms)

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. If a study patient experiences elevated alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≥5 × upper limit of normal (ULN),

1. Abemaciclib should be held for patients in Arm A. Dose adjustments to the endocrine therapy and management of patients in Arm B will be at the discretion of the investigator, as clinically indicated.
2. For all patients, central hepatic chemistry (part of the hepatic kit) including ALT, AST, total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be tested within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing.
3. If the abnormality persists or worsens, hepatic monitoring tests in Appendix 7 should be performed using the central laboratory hepatic monitoring kit, clinical monitoring should be initiated in consultation with the Lilly CRP/CRS, and the hepatic monitoring CRFs should be completed (see Section 9.4.2.1).
4. Monitoring of ALT, AST, and total bilirubin should continue until levels normalize or return to approximate baseline levels. Refer to Table JPCF.7.2 for guidance on dose adjustments of abemaciclib for patients with ALT/AST increased, or for other abnormal liver tests follow guidance for non-hematologic toxicities.

If clinically indicated, consider hepatobiliary ultrasound to assess for gallstones or gallbladder disease.

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 10.3.5) can conduct additional analyses of the safety data.

9.4.2.1. Special Hepatic Safety Data Collection

If one or more of the following situations occur, there is a separate group of hepatic monitoring CRFs that must be completed related to hepatic function.

- A repeat value 3 to 5 days after initial finding of elevation of serum ALT/AST≥5 × ULN that persists or worsens
- discontinuation from study treatment due to a hepatic event or an abnormality of liver tests
- occurrence of a hepatic event considered to be an SAE.

9.4.3. Safety Monitoring: Renal Function for Abemaciclib

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C-calculated glomerular filtration rate. Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function (Appendix 3).

Dose adjustment (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for non-hematological toxicities (Table JPCF.7.2).

9.4.4. Safety Monitoring: Venous Thromboembolic Events (Both Arms)

Venous thromboembolic events comprise PEs and DVTs; the latter occurs most often in the leg, but other veins, such as in the arm and cerebral veins, can be affected (Di Nisio et al. 2016). In the metastatic breast cancer Phase 3 clinical trial programs (MONARCH 2 and MONARCH 3), VTEs were considered as AEs of special interest for abemaciclib. Additional data on VTE is available in the IB.

If a patient experiences a VTE during treatment with abemaciclib, the patient should be treated as clinically indicated. The patient should temporarily stop abemaciclib while anticoagulation is initiated. After approximately 2 weeks of anticoagulation, the investigator may decide to restart abemaciclib based on his/her clinical judgment that it is appropriate for the patient to resume dosing. For life-threatening (Grade 4) VTEs, abemaciclib should not be restarted until there is evidence of resolution of the VTE and a discussion with the Lilly CRP should occur prior to restarting abemaciclib. Refer to Appendix 12 for guidance on the management of patients on abemaciclib who experience a VTE while on study.

Data on all VTEs (DVT or PE) will be collected and some events may be adjudicated by an external Clinical Events Committee (CEC). The role of the CEC is to adjudicate defined clinical events, in a blinded, consistent, and unbiased manner throughout the course of a study. The importance of the CEC is to ensure that all events that have been reported to the CEC are judged uniformly by a single group, using the same definition adjudicated.

9.4.5. Safety Monitoring: ILD/ Pneumonitis (Both Arms)

ILD/pneumonitis has been identified as an adverse drug reaction for abemaciclib. Additional information is available in the IB.

Ask your patients to report any new or worsening respiratory symptoms such as cough, dyspnea, fever, and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging such as high resolution computed tomography (HRCT), broncheoalveolar lavage, and biopsy as clinically indicated.

Refer to Table JPCF.7.2 for guidance on dose adjustments of abemaciclib for patients with ILD/pneumonitis (see Appendix 9 for CTCAE grades).

9.5. Pharmacokinetics

Pharmacokinetic samples will be collected in a subset of approximately 20% of patients from Arm A as shown in Appendix 6. Blood samples will be used to determine the concentrations of abemaciclib and its metabolites LSN2839567 and LSN3106726.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon by the investigator and Lilly.

Bioanalytical samples collected to measure abemaciclib concentrations will be retained for a maximum of 1 year following the last patient visit for the study.

9.6. Pharmacodynamics

See Section 9.8.

9.7. Pharmacogenomics or Genetics

CCI

[redacted]

CCI [redacted]

9.8. Biomarkers

CCI [redacted]

9.8.1. Samples for Ki-67 IHC Testing

The tissue sample must be from a FFPE CCI [redacted] block, may be either a tissue block (preferred) or fresh serially cut unstained sections, cut at 4-5 micron thickness. Cytological samples and fine-needle aspiration specimens are not acceptable. Tumor tissue specimens must have adequate evaluable tumor cells for a central laboratory to perform assessment for Ki-67 status. Due diligence should be used to ensure that tumor specimens (not a normal adjacent or a tumor margin sample) are provided. An associated pathology report may also be requested to be sent with the samples.

Tumor specimens submitted as an FFPE tissue block will be returned to the site, either at the end of study or upon request. For Cohort 2, FFPE blocks may be returned to the site immediately if the patient is deemed not eligible exclusively based on Ki-67.

Details for the handling and shipping of tumor samples will be provided in a separate document provided by the sponsor.

The tumor tissue samples for central Ki-67 testing will be coded with the patients' number and stored for up to a maximum of 15 years after the last patient visit for the study, unless local regulations and/or ERBs impose short time limits, at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by the investigative site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

CCI [redacted]

Cohort 1

Patients in Cohort 1 are not required to submit a tissue sample to the Study JPCF central laboratory for Ki-67 testing prior to randomization, but a sample will be requested, where available, to support the secondary analysis related to Ki-67.

Cohort 2

Patients in Cohort 2 must submit an untreated breast tissue sample to the Study JPCF central laboratory for central determination of Ki-67 status to determine eligibility (tissue should be submitted within one month of signing the consent). The sample will be tested using the investigational in vitro diagnostic medical device, pharmDx Ki-67 Kit, manufactured by Dako, as described in Section 3.2.1.

9.8.1.1. Ki-67 Analysis for Secondary Objective

Central Ki-67 testing will use breast tumor tissue obtained prior to any exposure to systemic therapy. For patients who previously received neoadjuvant systemic therapy, tumor tissue is to be obtained from initial diagnostic biopsy. For patients who had definitive breast surgery as their initial treatment (that is, no prior systemic therapies), tumor tissue can be either from definitive surgery specimen or initial diagnostic biopsy.

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[redacted]

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[redacted]

[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI

[redacted]

9.9. Health Economics

9.9.1. Health Outcomes

The self-reported questionnaires will be administered as shown in the Schedule of Activities (Section 2) in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

Included in this study are questionnaires to evaluate the patient-reported general health-related quality of life (HRQoL) effects of cancer and the specific effects associated with endocrine therapy with or without the addition of abemaciclib. Also evaluated are self-reported health dimensions and health status used to conduct decision modeling for health economic evaluations.

At each time point identified in the Schedule of Activities (Section 2), a paper copy of each questionnaire should be administered to the patient prior to extensive interaction with site staff, beginning with the most general HRQoL assessment (the Functional Assessment of Cancer Therapy - Breast (Version 4) [FACT-B]) followed by the Functional Assessment of Cancer Therapy - Endocrine Symptoms (Version 4) (FACT-ES) subscale. Thereafter, the symptom-specific fatigue subscale questionnaire should be administered, and followed by the 2 cognitive items and 3 bladder items. Lastly, the EuroQol five-dimension five-level questionnaire (EQ-5D-5L) is administered.

The questionnaires should always be completed in the specified order with the FACT/Functional Assessment of Chronic Illness Therapy (FACIT) content administered first followed by administration of the EQ-5D-5L. Following the ordering of general content to the specific content, the FACT/FACIT booklet/workbook will be sequenced as follows:

1. The FACT-B (which includes the FACT-G 27 well-being measures—the most general items/constructs—followed by breast cancer-specific 10-item subscale)
2. Starting on a new sheet, FACT-ES subscale

3. Starting on a new sheet, Functional Assessment of Chronic Illness Therapy - Fatigue (Version 4) [FACIT-F] subscale
4. Starting on a new sheet, a single sheet of additional concerns
   a) The 2 cognitive items, followed by
   b) The 3 bladder items
5. EQ-5D-5L

All the FACT/FACIT questionnaires, subscales, and items are scaled using a 5-point Likert rating ranging from 0 'not at all' through 4 'very much'. The recall period is the past 7 days. It usually takes 2 to 3 minutes to complete 10 questions.

9.9.1.1. General Well-being and Breast Cancer Assessment (FACT-B)

The 37-item FACT-B, which consists of the 27-item FACT-G and the 10-item breast cancer patient additional concerns subscale, was included to evaluate HRQoL in this adjuvant setting (Brady et al. 1997).

9.9.1.2. Endocrine Therapy and Fatigue Assessment (FACT-ES, 5 FACIT Library Items, FACIT-F)

Comprising 19 items, the FACT-ES (for patients with Endocrine Symptoms Version 4) was designed to be coadministered with the FACT-B (Fallowfield et al. 1999).

According to Fallowfield et al (1999), the 27-item FACT-G also includes 4 ET items (sleep, fatigue, nervousness, and nausea). Given the potential of abemaciclib adjuvant treatment to cause fatigue, also included in this study is the 13-item FACIT-F subscale (Yellen et al. 1997).

Bladder control and cognitive symptoms are often associated with ET, as was shown in the development of the Breast Cancer Prevention Trial (BCPT) Symptom Scales questionnaire (Stanton et al. 2005; Cella et al. 2008). Therefore, 3 items have been added for bladder control and 2 items have been added for cognitive symptoms, thereby updating the FACT-ES content coverage to match that reported in the BCPT research. These items were sourced from the FACIT item library (Functional Assessment of Chronic Illness Therapy Item Library Version 2). The 3 bladder items are:

- trouble controlling urine,
- more frequency than usual, and
- limiting activities.

The cognitive items are listed in the FACIT system as memory items and include:

- trouble remembering things and
- difficulty thinking clearly (remembering, concentrating).

9.9.1.3. EQ-5D-5L

EuroQol five-dimension five-level questionnaire is used to characterize overall health status by the evaluation of 5 health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a single visual analog scale (VAS) quantitative measure of health on a scale of 100 to 0 ranging respectively from "the best health you can imagine" and "the worst health you can imagine." This single index score can be used as for quality of life adjustment in

the estimation of quality-adjusted life-years for use in cost-effectiveness analyses. The VAS score, based on the patient's self-rated health today, serves to compliment the EQ-5D-5L single index score. (EuroQol 2017). The EQ-5D-5L is assessed using a daily recall period (that is, the recall period is "today") and completion time typically ranges from 2 to 3 minutes.

9.9.2. Resource Utilization

Utilization data overall and by arm will be summarized descriptively by category (for example, transfusions, antidiarrheal treatments, and hospitalization days) as appropriate.

10. Statistical Considerations

10.1. Sample Size Determination

The study will be powered to approximately 85% assuming an IDFS hazard ratio of .73 at a cumulative 1-sided alpha of .025. This requires approximately 390 events from across Cohort 1 and Cohort 2 by the time of the primary analysis after accounting for the interim efficacy and futility analyses described in Section 10.3.1.1. The number of patients required to observe approximately 390 events was calculated using Cytel East 6 and the following additional assumptions about pooled population in the two cohorts:

- Patients will enroll at a rate of 2, 8, 32, 60, 102, 140, 164, 188, 198, 206, 218, 238, 256, 260/month for the first 14 months, respectively, and then kept at 276/month for the remainder of the enrollment period.
- The time from first patient randomized to the observation of approximately 390 events will be approximately 4 years under the alternative hypothesis (hazard ratio of .73).
- The probability of a patient dropping out over the first 5 years following randomization is 10%.
- The 5-year IDFS rate for the control arm is 82.5%.

Under these assumptions, 4580 patients will be enrolled.

Patients will be randomized 1:1, within each cohort, using the following stratification factors:

- Prior treatment: neoadjuvant chemotherapy vs adjuvant chemotherapy vs no chemotherapy
- Menopausal status: premenopausal vs postmenopausal (menopausal status to be determined by investigator and based upon the patient's status at the time of diagnosis)
- Region: North America/Europe vs Asia vs Other

If a patient received both neoadjuvant and adjuvant chemotherapy, the patient will be stratified as neoadjuvant chemotherapy. Male patients will be stratified as postmenopausal at the time of randomization.

10.2. Populations for Analyses

The following populations will be defined for this study:

Intent-to-Treat (ITT) population: will include all randomized patients in Cohort 1 and Cohort 2. The ITT analysis of efficacy data will consider allocation of patients to treatment groups as randomized and not by actual treatment received. This population will be used for baseline, efficacy, and health economics analyses.

Safety or Randomized and Treated (RT) population: will include all randomized patients in Cohort 1 and Cohort 2 who received any quantity of study treatment. The safety evaluation will be performed based on the study regimen a patient actually received, regardless of the arm to

which he or she was randomized. The safety population will be used for all dosing/exposure, safety, and resource utilization analyses.

Ki-67 High (KI67H) population: will include all randomized patients in Cohort 1 and Cohort 2 with a centrally assessed Ki-67 index ≥20%. Secondary efficacy analyses will be performed on this population.

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Pharmacokinetic population: will include a subset of approximately 20% of patients randomized to Arm A who received at least 1 dose of abemaciclib and have at least 1 post-baseline evaluable PK sample.

10.3. Statistical Analyses

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

All tests of treatment effects will be conducted at a 1-sided alpha level of .025, unless otherwise stated. Unless otherwise stated, all confidence intervals (CIs) will be given at a 2-sided 95% level.

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. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1. Efficacy Analyses

10.3.1.1. Invasive Disease-Free Survival

The primary endpoint of this study is IDFS as defined by the STEEP System (Hudis et al. 2007). Invasive disease-free survival time is measured from the date of randomization to the date of first occurrence of:

3. ipsilateral invasive breast tumor recurrence
4. regional invasive breast cancer recurrence
5. distant recurrence
6. death attributable to any cause

7. contralateral invasive breast cancer
8. second primary non-breast invasive cancer

Patients for whom no event has been observed will be censored on the day of their last assessment for recurrence or date of randomization if no post-baseline assessment for recurrence occurred. The detailed censoring rules are described in Table JPCF.10.1.

Table JPCF.10.1. Rules for Determining Date of Event or Censor for Invasive Disease Free Survival

Situation	Date of Event or Censor	Event / Censor
IDFS event	Date of earliest IDFS event	Event
No IDFS event	Date of last assessment for recurrence	Censored
Unless		
No post-baseline disease recurrence assessment	Date of randomization	Censored
IDFS event documented after more than 12 months (+ 28 days)* following the last disease recurrence assessment or randomization (whichever is later)	Date of last assessment for recurrence prior to the documented IDFS event, or date of randomization (whichever is later)	Censored

*12 months (+28 days) is the longest allowed interval between visits in long-term follow up period after Year 5 defined by the schedule of activities

Abbreviation: IDFS = invasive disease-free survival.

The IDFS analysis to test the superiority of abemaciclib plus standard endocrine therapy to standard endocrine therapy will be performed on the ITT population and will use the log-rank test stratified by randomization factors. The futility analysis for IDFS will be conducted when approximately 130 events have been observed in ITT population. Futility should be declared if the observed IDFS hazard ratio is greater than 1.05. There are 2 planned efficacy interim analyses and 1 planned final analysis for IDFS in this study, which will be performed after approximately 195, 293, and 390 events have been observed in the ITT population. The cumulative 1-sided alpha will be controlled at .025, with an alpha split of 0.00000001 for the futility analysis and 0.02499999 for the planned efficacy analyses. The cumulative 1-sided type I error rate of .02499999 for the 2 planned efficacy interim analyses and 1 planned final analysis will be maintained using the Lan-Demets method (Demets and Lan, 1994). Specifically, the alpha spent at each efficacy interim analysis will be based on the exact number of IDFS events observed using the following O'Brien-Fleming type stopping boundary:

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

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. At the first efficacy interim analysis, the nominal 1-sided alpha level will be .0015 if exactly 195 IDFS events are observed. At the second efficacy interim analysis, the nominal 1-sided alpha level will be .0092 if exactly 293

IDFS events are observed. If the analyses are performed at exactly 195, 293, and 390 events, then the 1-sided boundary p-value at the final analysis will be .0220.

The efficacy and futility boundaries and properties of the design are described in Table JPCF.10.2.

Table JPCF.10.2. Efficacy Information

Analysis Point	Approximate Number of IDFS Events	Hazard Ratio for Futility	One-sided Boundary p-value for Efficacy	Cumulative Power Under H_1
Futility	130	1.05	N/A[a]	N/A
Interim 1	195	N/A	.0015	.222
Interim 2	293	N/A	.0092	.634
Final	390	N/A	.0220[b]	.861

Abbreviations: IDFS = invasive disease-free survival; N/A = not applicable.

[a] An arbitrary alpha split of 0.00000001 is applied at the futility analysis.

[b] Dependent on the actual number of events observed at each analysis.

In addition to the analysis described above, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the IDFS curves as well as IDFS rates at every 12 months for each treatment group. Also, a stratified Cox proportional hazard model (Cox 1972) with treatment as a factor will be used to estimate the hazard ratio and corresponding 95% CI with Wald's test p-value after adjusting for the same randomization variable specified for the primary analysis. An additional unstratified Cox regression model will be employed to explore the effects of prognostic variables, such as the stratification variables and intrinsic/extrinsic factors.

10.3.1.2. Overall Survival

Overall survival is defined as the time from randomization until death from any cause. Details concerning OS analyses can be found in the SAP.

10.3.1.3. Distant Relapse-Free Survival

Distant relapse-free survival is defined as the time from randomization to distant recurrence or death from any cause, whichever occurs first. Details concerning DRFS analyses can be found in the SAP.

10.3.1.4. Analyses of Efficacy in Other Populations

Details concerning analyses of efficacy in KI67H (Ki-67 high), CCI [redacted] populations can be found in the SAP.

10.3.2. Safety Analyses

All patients who receive at least 1 dose of any study therapy will be evaluated for safety and toxicity.

The Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0 (or higher) will be used when reporting AEs by MedDRA terms. The MedDRA Lower Level Term will be used in

the treatment-emergent computation. Treatment-emergent adverse events will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term within SOC.

Safety analyses will include summaries of the following:

- adverse events, including severity and possible relationship to study treatment
- serious adverse events, including possible relationship to study treatment
- adverse events leading to dose adjustments
- discontinuations from study treatment due to AEs or death
- treatment-emergent abnormal changes in laboratory values
- Treatment-emergent abnormal changes in vital signs

10.3.3. Other Analyses

10.3.3.1. Patient Disposition

A detailed description of patient disposition will be provided, including 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, as defined in the SAP, or discontinuing treatment or study (overall and by reason for discontinuation).

A summary of all important protocol deviations will be provided.

10.3.3.2. Patient Characteristics

Demographic data, disease characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported using descriptive statistics.

10.3.3.3. Concomitant Therapy

A summary of prior and concomitant medications by treatment arm will be reported.

10.3.3.4. Postdiscontinuation Therapy

The numbers and percentages of patients reporting postdiscontinuation anti-cancer therapies will be provided overall and by category and by drug name, where applicable.

10.3.3.5. Treatment Compliance

Dose omissions, dose reductions, dose intensity, and patient compliance for abemaciclib will be summarized for all treated patients in Arm A.

The actual cumulative dose of abemaciclib taken will be determined based on counting the number of capsules or tablets returned at each visit and subtracting that number from the number of capsules or tablets 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. Treatment compliance to abemaciclib will be measured as a percentage of the actual cumulative dose divided by the expected cumulative dose.

Dose intensity and treatment duration for standard endocrine therapy will be described for all treated patients in Arms A and B. For the on-treatment period, dose omissions for standard endocrine therapy will be summarized.

For Arm A, reasons for discontinuation of abemaciclib therapy will be summarized. For Arms A and B, reasons for discontinuation of standard endocrine therapy will be summarized.

10.3.3.6. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic analyses will be conducted on all patients who have received at least 1 dose of abemaciclib and have evaluable PK samples and sufficient dosing information. The goal is to complete PK analyses prior to interims, so that exposure-response analysis may be conducted as soon as the efficacy and safety response data are available. Measures will be taken to support the timely availability of the results of PK analyses. These measures will include periodic transfers for review of data relevant to PK analyses including dosing and bioanalytical results. In addition, an early snapshot will occur when sufficient PK samples from the PK population (approximately 20% of patients from Arm A) have been collected and analyzed. These snapshots will use aliased IDs so that the analysts will not know the actual patient ID. No safety or efficacy data will be included in the early snapshot PK datasets. Finally, this early PK analysis will be conducted by a separate team of PK analysts, independent of the core study team. Results will not be shared outside of the analysis team until the study team is unblinded.

In the early PK snapshot, mean population PK parameters for abemaciclib (and metabolites, if warranted) in plasma (for example, clearance, exposure, volume of distribution) and inter-individual PK variability will be computed using nonlinear mixed effect modeling (NONMEM).

The observed concentrations of abemaciclib may be summarized by time and dose.

Pharmacodynamic samples will be collected as specified in the Study Schedule and PK and PD Sampling Schedule (Appendix 6). Refer to these attachments (including footnotes) for important information about these samples and their collection.

Furthermore, PD data (such as neutrophil counts in blood) collected in this study may also be analyzed by means of NONMEM and connected to the population PK model in a PK/PD model.

Pharmacodynamic data from all patients undergoing PD assessments will be analyzed. CCI

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10.3.3.7. Health Outcome and Quality of Life Analyses

All health outcome, quality of life, and health utilization analyses will be described in the SAP.

10.3.4. Subgroup Analyses

A prespecified list of subgroups, including those defined by the stratification factors, will be identified in the SAP. The treatment effect within each subgroup will be summarized using methods specified in the SAP. Other subgroup analyses not specified in the SAP may be performed as deemed appropriate.

10.3.5. Interim Analyses

10.3.5.1. Safety Interim Analyses

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

Safety interim analyses will be reviewed by the DMC at a frequency described in the DMC charter, but no less than approximately every 6 months while patients are still in the on-study treatment period. The safety interim analyses will be conducted to evaluate the overall safety profile of abemaciclib when given in combination with standard endocrine therapy.

At each safety interim analysis, the DMC may recommend that 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 safety data at each safety 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 Senior Management Designee (SMD) and, if necessary, an Internal Review Committee (IRC).

A limited number of Lilly representatives external to the study team may have access to treatment assignments as required for evaluation of selected SAEs for determination of regulatory reporting.

10.3.5.2. Efficacy/Futility Interim Analyses

One futility analysis and two efficacy interim analyses are planned, as described in Section 10.3.1.1.

The efficacy interim analyses will be conducted to provide early efficacy information and could potentially result in early communication with regulatory agencies. The DMC should recommend the sponsor be unblinded if the analysis of IDFS is significant as described in Section 10.3.1.1 and any additional criteria specified in the DMC charter are met. The SMD may convene an IRC to review the DMC's recommendation prior to unblinding the study team.

The study will first be evaluated for futility. While the study may be stopped for futility at this analysis, the sponsor has no intent to stop the study at the two efficacy interim analyses, and all patients will continue follow-up for IDFS and OS until study completion. 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. If the DMC makes a recommendation counter to this, for example, the DMC recommends crossing all patients over to the experimental treatment, Lilly will consult the FDA before any action is taken, as well as other regulatory agencies if deemed appropriate.

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

Unblinding details are specified in the unblinding plan.

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Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE 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
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BCPT	Breast Cancer Prevention Trial
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
CAP	College of American Pathologists
CDK4	cyclin-dependent kinase 4
CDK6	cyclin-dependent kinases 6
CEC	Clinical Events Committee
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
collection database	a computer database where clinical trial data are entered and validated
CRF	case report form
CRP	Clinical Research Physician: an individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist (CRS), global safety physician, or other medical officer.
CRS	Clinical Research Scientist; also see CRP definition
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	ductal carcinoma in situ

DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRFS	distant relapse-free survival
ECOG PS	Eastern Cooperative Oncology Group performance status
eDC	electronic data capture
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.
EQ-5D-5L	EuroQol five-dimension five-level questionnaire
ERB	ethical review board
FACT-B	Functional Assessment of Cancer Therapy - Breast (Version 4)
FACT-ES	Functional Assessment of Cancer Therapy - Endocrine Symptoms (Version 4)
FACIT	Functional Assessment of Chronic Illness Therapy
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue (Version 4)
FFPE	formalin-fixed paraffin-embedded
FNA	fine-needle aspiration
G-CSF	granulocyte colony-stimulating factor
GCP	good clinical practice
GMP	Good Manufacturing Practice
GPS	Global Patient Safety
HER2-	human epidermal growth factor receptor 2 negative
HR+	hormone receptor positive
HRQoL	health-related quality of life
IB	Investigator's Brochure
IBTR	ipsilateral breast tumor recurrence
ICF	informed consent form
ICH	International Conference on Harmonisation

IDFS	invasive disease-free survival
IHC	Immunohistochemistry
ILD	interstitial lung disease
interim analysis	An interim analysis is an analysis of clinical trial data 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, including products already in the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board
IRC	Internal Review Committee
ISH	in situ hybridization
ITT	intent-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.
CCI [redacted]	[redacted]
IV	Intravenous
IWRS	interactive web-response system
KI67H population	Ki-67 High population: all randomized patients in Cohort 1 and Cohort 2 with centrally assessed Ki-67 index ≥20%
LCIS	lobular carcinoma in situ
Lilly	Eli Lilly and Company
LTFU	long-term follow-up
MATE	multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NONMEM	nonlinear mixed effect modeling
OS	overall survival
pCR	pathological complete response

PD	pharmacodynamic(s)
PET	positron emission tomography
PK	a subset of approximately 20% of randomized patients from Arm A who received at least 1 dose of abemaciclib and have at least 1 postbaseline evaluable PK sample
PK	Pharmacokinetic
pRb	phosphorylated retinoblastoma
PRO	patient-reported outcome
randomize	the process of assigning patients to an experimental group on a random basis
Rb	Retinoblastoma
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
CCI	[redacted]
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.
screen failure	a patient who does not meet one or more criteria required for participation in a trial
SMD	Senior Management Designee
SOC	System Organ Class
study drug	abemaciclib
study treatment	monarchE protocol defines study treatment as abemaciclib and /or ET during the first 2 years of treatment. The first dose of study treatment is the first dose of either abemaciclib or endocrine therapy following randomization.
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
topo	topoisomerase
ULN	upper limit of normal

VAS	visual analog scale
VTE	venous thromboembolic event

Appendix 2. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the potential risks and benefits of participating in the study,
- ensuring that informed consent is given by each patient. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study procedures and prior to the administration of study treatment,
- 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.

Ethical Review

Documentation of ERB/IRB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs/IRBs, before it is used at the investigative site(s). All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

The study site's ERBs/IRBs should be provided with the following:

- the current abemaciclib IB and updates during the course of the study
- the ICF
- relevant curricula vitae

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
- applicable ICH GCP Guidelines
- applicable laws and regulations

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

Investigator Information

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

Protocol Signatures

Lilly'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.

Final Report Signature

An investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

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

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 CRFs, 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 CRF 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.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs/IRBs with direct access to original source documents.

Data Capture System

An eDC system will be used in this study. The site maintains a separate source for the data entered by the site into Lilly-provided eDC system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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. Paper

documentation provided by the patient may include, for example, a paper questionnaire to collect patient-reported outcome measures (for example, a rating scale).

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 3. Clinical Laboratory Tests

Clinical Laboratory Tests	
Hematology - central laboratory[a]	
Leukocytes (WBC)	Erythrocytes (RBC)
Neutrophils[b]	Hemoglobin
Lymphocytes	Hematocrit
Monocytes	Mean corpuscular volume
Eosinophils	Mean corpuscular hemoglobin concentration
Basophils	Platelets
Clinical Chemistry - central laboratory[a]	
Serum Concentrations of:	
Alanine aminotransferase	Calcium
Albumin	Chloride
Alkaline phosphatase	Creatinine
Aspartate aminotransferase	Potassium
Bilirubin, direct	Protein, total
Bilirubin, total	Sodium
Blood urea nitrogen or blood urea	
Renal Panel - central laboratory (included in chemistry)	
Cystatin-C - central laboratory (included in chemistry)	
Pregnancy Test (for female patients of childbearing potential) - local laboratory	
Serum pregnancy test	
Ki-67 - central laboratory	

Abbreviations: RBC = red blood cell; WBC = white blood cell.

[a] Enrollment and treatment decisions may be based on local laboratory results. A duplicate sample must still be sent to the central laboratory. Differences between these samples will not constitute a protocol deviation.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be reported together.

Appendix 4. Highly Effective Methods of Contraception for Patients of Reproductive Potential

Patients with reproductive potential (that is, non-postmenopausal patients) are instructed to use highly effective contraceptive methods. The choice of the most effective and appropriate contraception method is up to the investigator's judgment after discussion with the patient, taking into account age, pregnancy and other gyneco-obstetrical history, sexual activity, patients' preference, acceptance of the contraception method, and potential adherence.

In patients with breast cancer, the use of estrogen-based hormonal contraception (includes the hormonal IUDs) is contraindicated, and the effect of progestin-based hormonal contraception remains unclear.

The Clinical Trial Facilitation Group has defined highly effective methods of contraception.[1]

Highly effective methods include the following:

- intrauterine device
- bilateral tubal occlusion
- vasectomized partner[2]
- sexual abstinence[3]

If the highly effective contraceptive methods are contraindicated or strictly declined by the patient, or in the event of sexual activity of low frequency, a combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods) is also considered an acceptable birth control method.

Local regulation/guidelines are to be followed with regard to highly effective birth control method, if more restrictive.

[1]Clinical Trial Facilitation Group. Recommendations related to contraception and pregnancy testing in clinical trials. September 2014. Available at: http://www.hma.eu/fileadmin/dateien/ Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_ Contraception.pdf. Accessed May 02, 2016.

[2]Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[3]In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Appendix 5. Omitted

Appendix 6. Pharmacokinetics/Genetics/Biomarkers Sampling Schedules

It is essential that the exact date and time of dose administration for the dose prior to PK sampling is recorded in the CRF based on patient interview. The exact date and time of collection of each venous blood sample must also be recorded on the laboratory requisition.

Due to practical and logistical concerns, some deviation from the specified sampling is possible. Sites should keep in mind that drawing the sample and recording the actual time on the appropriate form are of principal importance. Differences from the time specified in the protocol are not considered protocol deviations as long as samples are collected and accurate dates and times are recorded in a timely manner on the appropriate forms.

Sampling Schedule for Pharmacokinetics—Arm A Cohorts 1 & 2

PK Sample Number	Visit (V)	PK Sampling Time[a]
1	V01	2 h after abemaciclib dosed in clinic
2	V03	Any time after abemaciclib dosing
3	V05	Any time after abemaciclib dosing
4	V06	Any time after abemaciclib dosing

Abbreviation: PK = pharmacokinetic.

[a] Samples of approximately 2 mL of whole blood will be drawn for measurement of concentrations of abemaciclib and its metabolites.

Sampling Schedule for Genetics/Biomarkers

Sample	Collection Time Point	Comment
Tumor tissue for central Ki-67 eligibility confirmation (Cohort 2 only)	Need untreated breast tumor tissue submitted prior to randomization	For patients not eligible based on nodal status, tumor size, or grade
Tumor tissue for central Ki-67 (Cohort 1)	Need untreated breast tumor tissue submitted as soon as possible following randomization	Sample not mandatory for randomization, but will be requested
[redacted]	[redacted]	CCI
[redacted]	[redacted]	CCI
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	CCI	

CCI

Appendix 7. 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 CRP/CRS.[d]

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
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	
Alanine aminotransferase	**Recommended Autoimmune Serology**
Aspartate aminotransferase	Anti-nuclear antibody[a]
Gamma-glutamyl transferase	Anti-smooth muscle antibody[a]
Creatine phosphokinase	Anti-actin antibody[a]

Abbreviations: CRF = case report form; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

a Assayed by Lilly-designated laboratory.

b Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

c Reflex/confirmation dependent on regulatory requirements and/or testing availability.

d Consider hepatobiliary ultrasound to assess for gallstones or gallbladder disease.

Appendix 8. Protocol JPCF Inducers and Strong Inhibitors of CYP3A

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

Strong Inducers of CYP3A
Carbamazepine
Dexamethasone
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St John's wort

Moderate Inducers of CYP3A
Bosentan
Lenisurad
Modafinil
Primidone
Telotristat ethyl

Strong Inhibitors of CYP3A
Aprepitant
Ciprofloxacin
Clarithromycin
Conivaptan
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Posaconazole
Troleandomycin
Verapamil

Appendix 9. Protocol JPCF CTCAE 4.03 Definitions

Diarrhea will be evaluated in this study using the criteria proposed by 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 of ≥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					

ILD/pneumonitis will be evaluated in this study using the criteria proposed by CTCAE v4.0 revised: CTCAE 4.03–June 14, 2010: Respiratory, thoracic and mediastinal disorders.

Respiratory, Thoracic, and Mediastinal Disorders					
Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: a disorder characterized by inflammation focally or diffusely affecting the lung parenchyma					

Appendix 10. Protocol JPCF Breast Cancer Recurrence and Other Cancer Events

General instructions

- Documentation of a breast cancer recurrence requires meeting at least one of the criteria defined below. If there is suspicion of recurrence, this must be confirmed by imaging or by cytological/histopathological assessment (biopsy/FNA), as described in Table APP.10.1.
- Tumor marker evaluations alone do not document breast cancer recurrence.
- Treatment of a breast cancer recurrence or second primary cancer will be at the discretion of the investigator.

Table APP.10.1. Definitions for monarchE Endpoints

Endpoint	Invasive Ipsilateral Breast Tumor Recurrence	Local/Regional Invasive Recurrence	Distant Recurrence	Death from Any Cause	Invasive Contralateral Breast Cancer[a]	Second Primary Non-Breast Invasive Cancer[b]
Overall survival[d]				X		
Invasive disease-free survival[d]	X	X	X	X	X	X
Distant relapse-free survival[d]			X	X		
Confirmation requirements[c]	Biopsy	Biopsy/FNA	Biopsy/FNA or imaging		Biopsy	Biopsy/FNA or imaging

Abbreviations: DCIS = ductal carcinoma in situ; FNA = fine needle aspiration; LCIS = lobular carcinoma in situ.

a The term "contralateral invasive breast cancer" is preferred to "second primary breast cancer" as it is less ambiguous. Ipsilateral invasive breast cancers are presumed to be a recurrence.

b This excludes squamous or basal cell skin cancers or new in situ carcinomas of any site like ipsilateral or contralateral DCIS/LCIS.

c If bone is the only site of disease, imaging must be performed to confirm recurrence.

d Hudis et al. 2007.

Local Recurrence: Invasive Ipsilateral Breast Tumor Recurrence

An ipsilateral breast tumor recurrence (IBTR) event is defined as invasive breast cancer in the ipsilateral breast parenchyma or invasive breast cancer in the skin of the breast or the chest wall occurring after lumpectomy/mastectomy.

Acceptable methods for confirming local recurrence include core, incisional, or excisional biopsy. Cytology alone will not be adequate to establish IBTR.

Regional recurrence

Regional recurrence is defined as the development of tumor in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular, and/or ipsilateral axillary nodes, as well as the soft tissue of the ipsilateral axilla, following surgery. Recurrence must be confirmed by biopsy or cytology. However, if a patient meets criteria for distant metastatic disease, results of clinical exams alone will be sufficient to document regional recurrences.

Distant recurrence

Distant recurrence is defined as evidence of tumor in all areas other than the ones qualifying for local/regional recurrence as described above. **The first distant recurrence after an event other than distant recurrence or death, must be reported.**

- **Skin, Subcutaneous Tissue, and Lymph Nodes (Other Than Local or Regional)**

  Acceptable methods for confirming recurrence include positive cytology, aspirate or biopsy, or radiologic evidence of metastatic disease.

- **Bone Marrow**

  Acceptable methods for confirming recurrence include positive cytology, aspirate, biopsy, or MRI scan.

- **Lung**

  Acceptable methods for confirming recurrence include: (i) positive cytology, aspirate, or biopsy, or (ii) radiologic evidence of multiple pulmonary nodules that are judged to be consistent with pulmonary metastases.

  Note: If a solitary lung lesion is found and no other lesions are present on lung tomograms, computed tomography (CT) scan, or MRI scan, further investigations, such as biopsy, needle aspiration, positron emission tomography (PET)-CT scan, or PET scan, should be performed. Proof of neoplastic pleural effusion must be established by cytology or pleural biopsy.

- **Skeletal**

  Acceptable methods for confirming recurrence include: (i) x-ray, CT, or MRI evidence of lytic or blastic lesions consistent with bone metastasis, (ii) biopsy proof of bone metastases, or (iii) PET-CT scan, or PET scan clearly positive for bone metastases. Where a positive bone scan finding is the only evidence of progression, the presence of bone scan lesions needs to be confirmed by CT, MRI, or x-ray.

  Note: If the diagnosis is equivocal by bone scan or radiologic evaluation, a biopsy is strongly recommended. A bone scan with uptake limited to joints or in

a recent area of trauma (surgical or otherwise) cannot be used as a criterion for breast cancer recurrence.

- **Liver**

  Acceptable methods for confirming recurrence include: (i) abdominal CT scan, liver scan, ultrasound, MRI, PET-CT scan, or PET scan consistent with liver metastases, or (ii) liver biopsy confirmation of the metastatic disease.

  Note: If the radiologic findings are not definitive (especially with solitary liver nodules), a liver biopsy is recommended; however, if a biopsy is not performed, serial scans must be obtained to document stability or progression.

- **Central Nervous System**

  Acceptable methods for confirming recurrence include: (i) positive CT scan, PET-CT scan, PET scan, or MRI scan, usually in a patient with neurological symptoms, or (ii) biopsy or cytology (for a diagnosis of leptomeningeal involvement).

Invasive Contralateral breast cancer

Contralateral breast cancer is defined as evidence of invasive breast cancer in the contralateral breast or chest wall. The diagnosis of a contralateral breast cancer must be confirmed by core, incisional, or excisional biopsy. Cytology alone will not be adequate to document a contralateral breast cancer.

Second primary cancer

Second primary cancer is defined as any ***invasive*** non-breast cancer other than squamous or basal cell carcinoma of the skin. The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

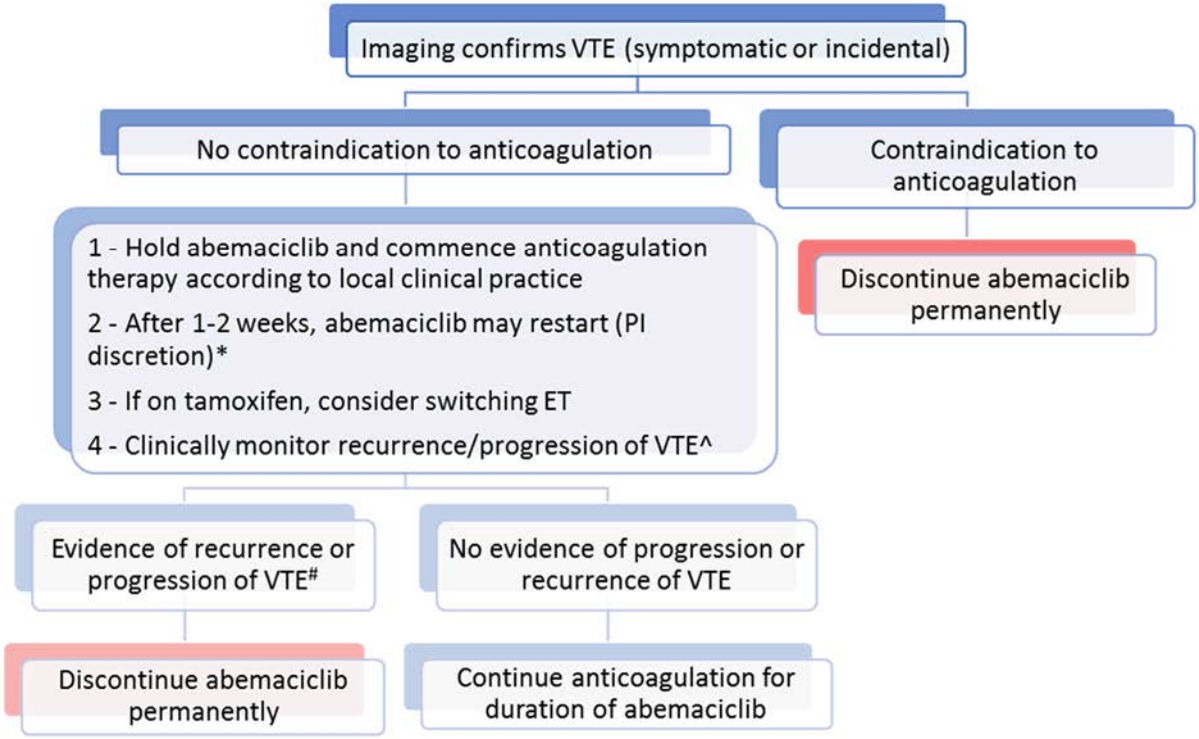
Documentation requested following death

- Autopsy reports should be secured whenever possible and should be retained in the patient's medical records.
- A copy of the death certificate should be retained in the patient's medical records if it is readily available or if it contains important cause-of-death information that is not documented elsewhere.

Appendix 11. Protocol JPCF: 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, for example, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair for more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Dead

Appendix 12. Protocol JPCF: Guidance for Treatment of Venous Thromboembolic Event



Additional things to consider

- A shorter duration of anticoagulation therapy may be considered in extenuating circumstances. Please contact the Lilly CRP/CRS to discuss.
- ESMO guidelines recommend changing endocrine therapy if a patient is on tamoxifen and develops a VTE
- If patient continues on tamoxifen, consider keeping the patient on anticoagulation for the duration of treatment with tamoxifen.

Abbreviations: CRP/CRS = clinical research physician/scientist; ET = endocrine therapy; PI = investigator; VTE = venous thromboembolic event.

* Patients with CTCAE grade 4 VTE should be stable, with clear clinical improvement and evidence of adequate anticoagulation before restarting abemaciclib.

^ Investigators should investigate exacerbation of existing (or development of new) VTE symptoms.

If the patient is not fully anticoagulated and experiences recurrence/progression of VTE, and the patient/investigator wishes to continue abemaciclib, please contact the Lilly CRP/CRS to discuss.

Figure App.12.1 Guidance for treatment of venous thromboembolic events for patients on abemaciclib

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