Protocol: I3Y-IN-JPEC(b)

A Single-Arm, Phase 4 Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, in Combination With Endocrine Therapy (Anastrozole/Letrozole or Fulvestrant) in Participants With Hormone Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative Locally Advanced and/or Metastatic Breast Cancer in India

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Title Page

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Protocol Number: I3Y-IN-JPEC

Amendment Number: b

Compound: LY2835219

Study Phase: Phase 4

Short Title: A Study of Abemaciclib in Combination with Endocrine Therapy (Anastrozole/Letrozole or Fulvestrant) in Participants with HR+, HER2- Locally Advanced and/or Metastatic Breast Cancer in India

Acronym: JPEC

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

CTRI Registration number: CTRI/2020/12/030021

Approval Date: Protocol Amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Medical Monitor Name and Contact Information will be provided separately.

Approval Date: 29-Sep-2021 GMT

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol amendment (b)	**See the protocol cover page**
Original Protocol	17 June 2020

Amendment [b]

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment addresses.

Section # and Name	Description of Change	Brief Rationale
Synopsis	The participant number was updated from 100 to 200.	As part of abemaciclib marketing authorization in India and related post-approval condition by the Indian MoH, Lilly was asked to do a Phase 4 study on 200 patients. Lilly proposed a study on 100 patients along with the rationale of global Phase 3 data. The study was started basis conditional approval from the Indian MOH. Basis the additional safety data on Phase 3 studies and Indian PSUR data, Lilly requested the Indian MoH to allow conducting the study with 100 enrolled patients; however, the MoH did not agree and recommended conducting the study in 200 patients. Hence, the protocol is being amended now to reflect 200 patients in the study.
1.2 Schema	Study schema has been amended for total number of participants and number of participants in each cohort	As per MoH recommendation to conduct the study in 200 patients to generate additional safety data in Indian population. (as specified above).
4.2 Scientific Rationale for Study Design	The participant number was updated from 100 to 200.	As per MoH recommendation to conduct the study in 200 patients to generate additional safety data in Indian population. (as specified above).
9.2 Sample Size Determination	The participant number was updated from 100 to 200 and, accordingly, the cohort size was changed from 25 to 50. The estimated incidence rate and 2-sided 95% CI table were updated.	Statistical calculations updated as per the change in the number of participants.

Abbreviations: CI = confidence interval; MoH = Ministry of Health; PSUR = periodic safety update report.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Single-Arm, Phase 4 Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, in Combination with Endocrine Therapy (Anastrozole/Letrozole or Fulvestrant) in Participants with Hormone Receptor Positive, Human Epidermal Growth Factor Receptor 2-Negative Locally Advanced and/or Metastatic Breast Cancer in India

Short Title: A Study of Abemaciclib in Combination with Endocrine Therapy (Anastrozole/Letrozole or Fulvestrant) in Participants with HR+, HER2- Locally Advanced and/or Metastatic Breast Cancer in India

Rationale:

Pivotal abemaciclib Phase 3 clinical trials I3Y-MC-JPBL (MONARCH 2) and I3Y-MC-JPBM (MONARCH 3) demonstrated that abemaciclib, a cyclin-dependent kinase (CDK), CDK4 and CDK6 inhibitor (CDK4&6), when used in combination with endocrine therapy (ET) significantly improved progression-free survival (PFS) and objective response rate (ORR) in patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced and/or metastatic breast cancer (MBC). While the safety of abemaciclib plus ET has been well characterized from these global Phase 3 studies, there is very limited information about the safety of abemaciclib in Indian breast cancer patients. This study will characterize the safety of abemaciclib in combination with ET in Indian patients with HR+, HER2- advanced and/or MBC.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety of abemaciclib in combination with ET (anastrozole/letrozole or fulvestrant)	• TEAEs (including SAE and AESI) per CTCAE criteria version 5.0
Secondary	
• To evaluate incidence of treatment discontinuation of abemaciclib	• Discontinuation of abemaciclib only due to an AE

Abbreviations: AE = adverse event; AES I= adverse events of special interest; CTCAE = Common Terminology Criteria for Adverse Events; ET = endocrine therapy; TEAE = treatment-emergent adverse events; SAEs = serious adverse events.

Overall Design:

This is a Phase 4, single-arm, cohort study of abemaciclib in combination with either an aromatase inhibitor (anastrozole or letrozole) or fulvestrant, in patients with HR+, HER 2- locally advanced and/or metastatic breast cancer. This study is designed to characterize the safety and tolerability of abemaciclib plus ET in Indian participants.

Disclosure Statement:

This is a single-group treatment study with 1 arm and no masking.

Number of Participants:

Approximately 200 participants will be enrolled in the study.

Intervention Groups and Duration:

There are two cohorts planned for the study.

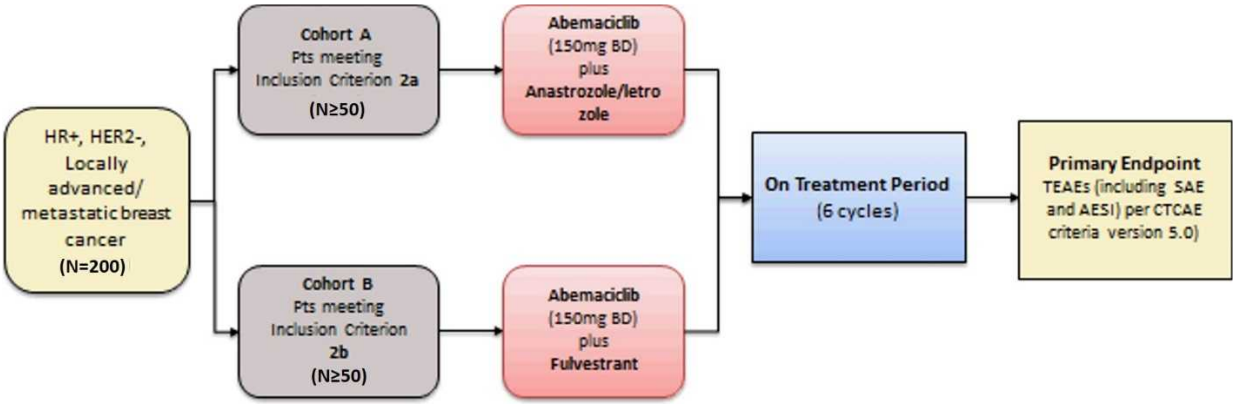
- Cohort A: abemaciclib 150 mg twice daily (BD) plus either anastrozole or letrozole
- Cohort B: abemaciclib 150 mg BD plus fulvestrant

Participants will receive 6 cycles of study intervention (total duration ~6 months) or less if a criterion for discontinuation is met prior to the completion of 6 cycles. Participants who completed the study after 6 cycles of treatment may continue to receive abemaciclib through a patient support program as per investigator's discretion.

Data Monitoring Committee:

No

1.2. Schema



Abbreviations: AESI = adverse events of special interest; CTCAE = Common Terminology Criteria for Adverse Events; HER2- = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive;

N = number of planned participants; TEAE= treatment emergent adverse events; SAEs= serious adverse events.

Note: Please refer to section 5.1 for a detailed information on inclusion criteria 2(a) and 2(b).

1.3. Schedule of Activities (SoA)

This section includes baseline, on- treatment, and post-discontinuation follow-up schedule of activities (SoAs)

Screening, On-Treatment and Post-Treatment Schedule of Activities

Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**End of Study Visit** [a]	**Post-Treatment Follow-up**	**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 to 6**	**Cycle 6**	**Short-Term Follow-Up** [b]	
Relative Day within Dosing Cycle & Visit Window (±n days)	**≤28**	**≤14**	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D28 (±3)**	**V801** (30 days +7)	
Documentation and Examination										
Informed consent	X									Written informed consent must be obtained prior to conducting any protocol-specific tests/procedures.
Inclusion and exclusion criteria	X									See sections 5.1 and 5.2
Medical history	X									Including assessment of preexisting conditions, historical illnesses, prior anticancer therapies (including systemic, local, and surgical), and habits (such as tobacco and alcohol use).
Prior and concomitant medication	X		X					X	X	At screening, record prior and concurrent medications. Record all premedications, supportive care, and concomitant medications including over-the-counter and analgesics use, continuously at every visit

									and throughout the study.
Physical examination	X	X	X	X	X	X	X	X	Perform prior to administering abemaciclib. Includes height (only at screening) and weight. Does not need to be repeated on

Screening, On-Treatment and Post-Treatment Schedule of Activities										
Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**End of Study Visit [a]**	**Post-Treatment Follow-up**	**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 to 6**	**Cycle 6**	**Short-Term Follow-Up [b]**	
Relative Day within Dosing Cycle & Visit Window (±n days)	**≤28**	**≤14**	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D28 (±3)**	**V801** (30 days +7)	
										Cycle 1 Day 1 if assessed at baseline ≤3 days prior to abemaciclib initiation. Additional exams should be performed as clinically indicated.
Vital signs		X	X	X	X	X	X	X	X	Perform prior to administering abemaciclib. Collect temperature, blood pressure, pulse, and pulse rate. Repeat if clinically indicated.
ECOG performance status		X	X		X		X	X	X	Does not need to be repeated on Cycle 1 Day 1 if assessed at baseline ≤3 days prior to abemaciclib initiation.
Other Clinical Assessments										
12-lead ECG	X							X	X	Single ECG performed locally. Participants should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Repeat if clinically indicated.

AE assessment	X	X	X	X	At baseline determine the stool frequency for each participant to ensure increase from baseline can be assessed per CTCAE throughout the study (see appendix 7). Collect continuously at every visit and throughout the study using CTCAE Version 5.0.

Screening, On-Treatment and Post-Treatment Schedule of Activities										
Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**End of Study Visit [a]**	**Post-Treatment Follow-up**	**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 to 6**	**Cycle 6**	**Short-Term Follow-Up [b]**	
Relative Day within Dosing Cycle & Visit Window (±n days)	**≤28**	**≤14**	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D28 (±3)**	**V801** (30 days +7)	
										See Section 8.3 for further details on AE and SAE reporting.
Laboratory Assessments										
Hematology		X	X	X	X	X	X	X	X	See Appendix 2 (Section 10.2). Does not need to be repeated on Cycle 1 Day 1 if assessed at baseline ≤3 days prior to abemaciclib initiation. Repeat if clinically indicated. Refer to Section 8.2.1.
Clinical chemistry		X	X	X	X	X	X	X	X	See Appendix 2 (Section 10.2). Does not need to be repeated on Cycle 1 Day 1 if assessed at baseline ≤3 days prior to abemaciclib initiation. Repeat if clinically indicated. Refer to Section 8.2.1.
Pregnancy test		X								A serum pregnancy test is required at baseline only for participants receiving ovarian suppression with a GnRH agonist. Pregnancy tests post baseline are per the investigator's discretion.

Screening, On-Treatment and Post-Treatment Schedule of Activities										
Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**End of Study Visit [a]**	**Post-Treatment Follow-up**	**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 to 6**	**Cycle 6**	**Short-Term Follow-Up [b]**	
Relative Day within Dosing Cycle & Visit Window (±n days)	**≤28**	**≤14**	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D28 (±3)**	**V801** (30 days +7)	
FSH and estradiol	X									Required only for women <55 years with amenorrhea for at least 12 months to confirm post-menopausal status
Tumor imaging	X		Every 12 weeks							**Imaging at Screening:** Imaging performed previously as part of routine care may be used provided these were performed within 12 weeks before Cycle 1 Day 1. **Imaging while On Treatment:** Imaging should be performed every 12 weeks according to local standards and if clinically indicated as per the investigator's judgment to determine disease progression. More frequent imaging is allowed as part of routine medical care.

Screening, On-Treatment and Post-Treatment Schedule of Activities										
Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**End of Study Visit [a]**	**Post-Treatment Follow-up**	**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 to 6**	**Cycle 6**	**Short-Term Follow-Up [b]**	
Relative Day within Dosing Cycle & Visit Window (±n days)	**≤28**	**≤14**	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D28 (±3)**	**V801** (30 days +7)	
Bone nuclear imaging (such as bone scan, PET scan or PET/CT)	X		As per standard of care							**Bone Imaging at Screening:** Imaging performed previously as part of routine care may be used provided these were performed within 12 weeks before Cycle 1 Day 1. **Bone Imaging while On Treatment:** Bone imaging should be performed according to local standards and if clinically indicated per the investigator's judgment to determine disease progression.
Assessment of progression (symptomatic and radiological as per local practice)			X		X		X	X		Participants discontinuing either abemaciclib or endocrine therapy prior to disease progression will continue to have scheduled assessments until documented radiographic or symptomatic progression per investigator's judgment.
Study Treatment										
Abemaciclib			Orally twice daily, on Days 1 through 28 of a 28-day cycle.							See Section 6.1.
Administer anastrozole or letrozole (Cohort A)			As per standard of care							See Section 6.1.
Administer fulvestrant (Cohort B)			As per standard of care							See Section 6.1.

Screening, On-Treatment and Post-Treatment Schedule of Activities										
Study phases	**Screening**		**On Treatment Cycle duration = 28 days**					**End of Study Visit [a]**	**Post-Treatment Follow-up**	**Instructions**
	Baseline		**Cycle 1**		**Cycle 2**		**Cycle 3 to 6**	**Cycle 6**	**Short-Term Follow-Up [b]**	
Relative Day within Dosing Cycle & Visit Window (±n days)	**≤28**	**≤14**	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D15** (±3)	**D1** (±3)	**D28 (±3)**	**V801** (30 days +7)	
Study intervention compliance assessment					X		X	X		Abemaciclib bottle(s), including any unused tablets, will be returned at the beginning of every cycle starting at Cycle 2 Day 1 and at abemaciclib discontinuation for drug accountability
Dispense and review patient diary			X	X	X	X	X	X		Review patient diary at each study visit for completion.

Abbreviations: AE = adverse events; D = day; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicular stimulating hormone GnRH = gonadotropin-releasing hormone; PET = positron emission tomography; SAEs = serious adverse events; V = visit.

[a] The End of Study visit is not required for participants discontinuing study treatment prior to completion of 6 cycles or for participants who complete 6 cycles but do not continue to receive abemaciclib. These participants must complete the Short-Term Follow-Up instead.

[b] Short-Term Follow-Up begins when the participant and investigator agree that the participant will no longer continue study treatment. The Short-Term Follow-Up is not required for participants who continue on abemaciclib (for example, in a patient support program) after the End of Study Visit.

2. Introduction

2.1. Study Rationale

Abemaciclib has been studied in combination with the nonsteroidal aromatase inhibitors (NSAIs) anastrozole or letrozole in hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer in study I3Y-MC-JPBM (MONARCH 3) and in combination with fulvestrant in I3Y-MC-JPBL (MONARCH 2). These 2 pivotal global studies showed a significant efficacy benefit and acceptable safety profile (Goetz et al. 2018; Sledge et al. 2017) and have led to the approval of abemaciclib by major global regulatory authorities for the treatment of patients with HR+, HER2- metastatic breast cancer (MBC) in combination with an NSAI as initial endocrine-based therapy and with fulvestrant following progression on endocrine therapy (ET).

In study I3Y-CR-JPBQ (JPBQ), a Phase 3 study of abemaciclib plus either NSAI or fulvestrant in HR+/HER2- locally locoregionally recurrent or MBC, patients were primarily enrolled in China, with limited numbers from Brazil, South Africa, and India (N=32). The study showed that the efficacy and safety profile of abemaciclib was consistent with the results of MONARCH 2 and 3 (Jiang et al. 2019, Abstract presented in European Society for Medical Oncology Congress [ESMO], 2019). While the safety of abemaciclib in combination with endocrine therapies has been well characterized in these global Phase 3 studies, there is only limited information from the JPBQ study about the safety of abemaciclib in MBC patients in India.

Study I3Y-IN-JPEC (hereafter referred to as Study JPEC) is a single-arm, open-label, cohort-based, Phase 4 study that will prospectively assess the safety of abemaciclib in combination with either anastrozole/letrozole (enrolled in cohort A) or fulvestrant (cohort B) in Indian patients with HR+, HER2- locally advanced and/or MBC.

2.2. Background

2.2.1. Metastatic Breast Cancer

Breast cancer is the most common malignancy in women worldwide, impacting 2.1 million women every year (Global Cancer Observatory [GCO], GLOBOCAN, 2018 published in International Agency for Research on Cancer [IARC], 2020), and accounts for the second highest number of deaths among women globally (Centers for Disease Control and Prevention [CDC], 2019).

In India, approximately 162 468 new cases of breast cancer (14% of all cancer cases) emerge annually, making it the most common cancer in women in India (GLOBOCAN 2018 published in International Agency for Research on Cancer [IARC]). Breast cancer cases are reported more in women from less developed countries than that of developed countries (883 000 vs 794 000 cases) (Ferlay et al. 2015). These findings can be corroborated with a significant rise in breast cancer related morbidities and mortalities in the Indian subcontinent (Malvia et al. 2017; Gupta et al. 2015; Babu et al. 2013; Balasubramaniam et al. 2013; Ali et al. 2011; Porter et al. 2009; Srinath et al. 2005).

Breast cancers are the least reported cancers in India, per literature. Though the nature of the breast cancer may not differ entirely from its counterparts in Western countries, the proportion of breast cancer distribution is different in India (Rangarajan et al. 2016).

Well-equipped private hospitals observe 80% of Grade III breast cancer, but overall Grade II cancers dominate the proportion, with 9.5% to 20% of Grade I breast cancer (Rangarajan et al. 2016). Varying reference patterns and a wide economic gap in the patient population in India are some of the major underlying reasons for paucity of information in breast cancers in India and provides an insight into the trends of breast cancer in India (Rangarajan et al. 2016).

While early-stage breast cancer is typically curable (Harbeck and Gnant, 2017), advanced breast cancer has a median overall survival rate of 2 to 3 years and a 5-year survival rate of approximately 25% (Cardoso et al. 2018). Metastatic breast cancer presents a poor prognosis in the Indian population, with a 5-year and 10-year overall survival rate of 22% and 5% (Gogia et al. 2019; Chopra, 2001). Approximately 1800 patients registered in the Indian breast cancer clinics from 2012 to 2018 were analyzed for the long-term outcome of MBC patients in India.

Hormone receptor positive status, oligometastasis, and good performance status, were associated with better outcomes in this study wherein most of the patients received chemotherapy followed by ET (Gogia et al. 2019).

Breast cancer treatment in India is highly varied in terms of health care standards. Despite major technological advancements in India, a large proportion of cancer patients either do not have access or cannot afford the treatment in India. It arises a need to develop safe and effective strategies that can be propagated on a country wide basis (Consensus Document for Management of Breast Cancer, Indian Council of Medical Research, 2016). The average population of breast cancer patients in India is a decade younger (48 to 53 years) than those in the Western countries (Kumar et al. 2018; Bustreo et al. 2016). This may be due to its population structure and its inherent bias against referral in India. The incidence of breast cancer increases with age and approximately 90% of sporadic breast cancers in India are associated with reproductive history, lifestyle, or environmental factors, primarily influencing their hormonal milieu (Consensus Document for Management of Breast Cancer, Indian Council of Medical Research, 2016).

More than 100 000 patients are treated for breast cancer every year in India (KhoKhar et al. 2012), but, only about 11 to 23% of patients (1000 patients) opt for breast-conserving treatment (BCT) (Narendra et al. 2011). The lower rate of BCT in Indian patients is reflective of the late- stage at presentation and lack of well-equipped BCT centers, radiation therapy, and pathology (Vishwakarma et al. 2019; Agarwal et al. 2008; Dinshaw et al. 2005; Raina et al. 2005). Indian women undergoing BCT are younger (<40 years), are higher grade, larger, HR negative tumors compared to the Western countries (Rangarajan et al. 2016). Low number of treatment facilities, lack of awareness, poor compliance to treatment, higher cost of treatment, and social stigma associated with the disease affects the effective management of breast cancer in India (Maurya and Brahmachari 2020). Resource constraints and limited availability of diagnostic tools (preoperative mammography etc.) has discouraged the use of effective breast cancer management in India (Rangarajan et al. 2016).

The Asian Society of Mastology (ASOMA), established in 2016 aims to improve the health care system in women with breast cancer in Asian countries. Sparsity of genetic counselling, molecular testing facilitates, and resource constraints are being considered for effective management of breast cancer in Asian countries (Srivastava et al. 2020).

Systemic treatment options for advanced breast cancer are largely determined by the presence (or absence) of HR and HER2. Recent advances in the treatment of HR+, HER2- advanced breast cancer have contributed to improved patient outcomes (Cardoso et al. 2018). Use of aromatase inhibitors in postmenopausal women is low and slowly increasing, however, ET is still the most widely used treatment for breast cancer in India (Agarwal et al. 2008). The trend of use of ET therapy continues to dominate developing nations, with increased use of ET in 45.7% premenopausal women and 83.5% in postmenopausal women in Iraq (Abd-Alhussain et al. 2020; Jeon et al. 2017; Bujis et al. 2009). Penetration of generics in Indian markets (paclitaxel generic, docetaxel generic etc.) for MBC is also gaining popularity. Some investigators from India, conducted a retrospective analysis of 393 patients who received generic versions of docetaxel, oxaliplatin, irinotecan, and gemcitabine. The median survival ranged to 47 months for patients with breast cancer (45% had metastatic disease) and 20% to 45% of patients reported serious adverse events (SAEs) (Lopes, 2013).

While NSAIs such as anastrozole and letrozole are the preferred initial treatment for the majority of patients with HR+, HER2- advanced breast cancer, ET resistance eventually develops, making patients unresponsive to standard ET approaches that target HR blockade (Flaum and Gradishar, 2018). In HR+ breast cancer, estrogen induces overexpression of cyclin D1, which in association with cyclin-dependent kinase (CDK), CDK4 and CDK6 (CDK4&6), promotes unregulated cell cycle progression. In breast cancer, cyclin D1/CDK4 has been shown to promote phosphorylation of the retinoblastoma (Rb) protein, cell proliferation, and tumor growth (Sherr 1996; Ortega et al. 2002). CDK4&6 inhibitors (such as abemaciclib, palbociclib, or ribociclib) work by preventing Rb phosphorylation and blocking progression from G1 into S phase of the cell cycle, thus leading to suppression of tumor growth in preclinical models following short duration of target inhibition (Sherr 1996; Ortega et al. 2002). In estrogen receptor (ER) positive breast cancer cell lines, sustained target inhibition by CDK4&6 inhibitors prevents the rebound of Rb phosphorylation and cell cycle re-entry, resulting in senescence and apoptosis (Sherr 1996; Ortega et al. 2002). In the clinic, CDK4&6 inhibitors combined with ET (NSAI or fulvestrant) have demonstrated greater efficacy compared with ET alone in patients with HR+, HER2- advanced breast cancer (Finn et al. 2015; Hortobagyi et al. 2016; Goetz et al. 2017; Sledge et al. 2017; Slamon et al. 2018; Turner et al. 2018).

Due to the remarkable efficacy in progression-free survival (PFS) and objective response rate ORR and their manageable side-effect profile associated with the addition of CDK4&6 inhibitors to ET, these agents have become the new standard of care for women with HR+, HER2- advanced breast cancer receiving first and subsequent lines of therapy (Flaum and Gradishar, 2018).

2.2.2. Abemaciclib

Abemaciclib is an oral selective and potent adenosine triphosphate-competitive inhibitor of CDK4&6 that is administered on a continuous dosing schedule.

CDK4&6 inhibitors are known to interact with D-type cyclins and stimulate proliferation. CDK4&6 - D-cyclin complex, regulates the cell cycle checkpoints (G1/S), through phosphorylation and inactivation of the Rb tumor suppressor protein. Alterations in CDK4&6 or cyclin D commonly occur in human cancers and can be explored from a therapeutic standpoint.

The inhibition of CDK4&6 (with a small molecule inhibitor) can prevent cell cycle progression (through G1 restriction point) thereby arresting tumor growth.

The clinical activity and safety of abemaciclib has been extensively studied in HR+, HER2- advanced breast cancer.

In the randomized, placebo-controlled MONARCH 2 Phase 3 study, the addition of abemaciclib to fulvestrant provided a significant improvement of PFS (16.9 months versus 9.3 months, hazard ratio 0.536; 95% CI: 0.445, 0.645; p<.0001), overall survival (OS) (46.7 months versus 37.3 months, hazard ratio 0.757; 95% CI, 0.606-0.945; p=.0137) and ORR (48.1% versus 21.3%; 95% CI: 42.6, 53.6; p<.001) compared to placebo plus fulvestrant in HR+, HER2- advanced or MBC patients who progressed during prior ET (Sledge et al. 2017; Sledge et al. 2020). Of note, the OS benefit was consistent across subgroups including patients with a poorer prognosis with visceral metastases and primary endocrine resistance (Sledge et al. 2020).

In the randomized, placebo-controlled MONARCH 3 Phase 3 study, the addition of abemaciclib to a NSAI as initial treatment of HR+, HER2− advanced or MBC patients provided a significant improvement of PFS (28.2 months versus 14.8 months; hazard ratio 0.540; 95% CI: 0.418 to 0.698; p=.000002) in the intent-to-treat population (N=493) and the ORR for patients with measurable disease (N=399, 80.9%) was 61.0% versus 45.5% (95% CI 37.0, 53.9; p=.003) compared to placebo plus NSAI (Johnston et al. 2019). The OS data, an important secondary end point of this study, are immature.

The most common adverse events of all grades for abemaciclib in the MONARCH 2 (plus fulvestrant) and MONARCH 3 (plus NSAI) were: diarrhea (86.4% and 82.3%), neutropenia (46.0% and 43.7%), nausea (45.1% and 41.3%), and fatigue (39.9% and 41.3%), respectively. Abemaciclib was discontinued for adverse events (AEs) in 15.9% of the cases in MONARCH 2 and 25.1% of patients in the abemaciclib arm discontinued any study intervention as the result of an AE in MONARCH 3 (Sledge et al. 2017; Johnston et al. 2019). A comprehensive safety analysis of abemaciclib-associated AEs from MONARCH 2 and 3 by Rugo et al. [Rugo et al., unpublished data] showed that the most common Grade ≥3 AE was neutropenia (25.4%), typically occurring within the first 2 cycles of treatment, and resolving with dose adjustments.

The decreasing incidence in subsequent cycles following abemaciclib dose adjustment indicated low recurrence. Clinically significant diarrhea (Grade ≥2) was reported for 42.8% of patients taking abemaciclib with a median time to onset of 1 week, and duration ranging from 6 to 12 days. Clinically important laboratory abnormalities included increased alanine aminotransferase (ALT) Grade ≥3 (4 to 6%) and increased aspartate aminotransferase (AST) Grade ≥3 (2 to 4%). The median time to onset for Grade ≥3 increased ALT in the abemaciclib arms was approximately 60 days in both studies and 185 days and 71 days for AST in MONARCH 2 and 3, respectively. Effects were reversible in both studies, as demonstrated by short duration of Grade ≥3 increased ALT and AST, with a median time to resolution (for all patients regardless of dose adjustments) from onset of approximately 2 weeks. Other clinically relevant AEs reported in these studies were any grade venous thromboembolic events (VTEs) (5 to 6%), and interstitial lung disease (ILD)/pneumonitis (2 to 5%).

Study JPBQ, where abemaciclib plus NSAI (cohort A) or fulvestrant (cohort B) was given in a predominantly Chinese HR+, HER2− locoregionally recurrent or MBC population, showed similar safety and tolerability results as in MONARCH2 and MONARCH3. However, the incidence of clinically significant diarrhea (Grade ≥2) was lower (28.8% reported for both

cohorts) likely due to the raised awareness and improved management in the JPBQ study [JPBQ Clinical Study Report, Zhang et al. unpublished data].

Abemaciclib is currently approved by major global regulatory authorities for the treatment of patients with HR+, HER2- advanced or MBC in combination with a NSAI as initial endocrine- based therapy and with fulvestrant following ET. In addition, abemaciclib is also approved as monotherapy for heavily pretreated (following ET and chemotherapy) HR+, HER2- MBC patients by the Food and Drug Administration (FDA) and other geographies including India.

While these results support the use of abemaciclib in combination with endocrine therapies for the treatment of advanced and/or MBC, the safety and tolerability has not been studied extensively in the Indian population. Study JPEC will assess the safety and tolerability of abemaciclib in combination with ET in Indian patients with HR+, HER2- locally advanced and/or MBC.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits, risks, SAEs, AEs of special interest (AESI) and reasonably anticipated AEs of abemaciclib is 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, may be found in the respective Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety of abemaciclib in combination with ET (anastrozole/letrozole or fulvestrant)	• TEAEs (including SAEs and AESIs) by per CTCAE criteria version 5.0
Secondary	
• To evaluate incidence of treatment discontinuation of abemaciclib	• Discontinuation of abemaciclib only, due to an AE

Abbreviations: AE = adverse event; AESI = adverse events of special interest; CTCAE = Common Terminology Criteria for Adverse Events; ET = endocrine therapy; TEAE = treatment-emergent adverse events; SAEs = serious adverse events.

4. Study Design

4.1. Overall Design

Study JPEC is a Phase 4, single-arm, cohort study of abemaciclib in combination with either a NSAI (anastrozole or letrozole) or fulvestrant, in patients with HR+, HER2- locally advanced and/or MBC. This study is designed to characterize the safety of abemaciclib plus ET in Indian patients.

Participants receiving initial endocrine-based therapy for advanced/MBC will be assigned to cohort A to receive abemaciclib in combination with anastrozole/letrozole. Participants who have received prior ET in the advanced/metastatic setting or relapsed while on/or within 1 year after ET in the adjuvant setting, will be assigned to cohort B to receive abemaciclib in combination with fulvestrant.

To evaluate the safety of abemaciclib in combination with anastrozole/letrozole or fulvestrant, AEs will be assessed throughout the study and the clinical safety laboratory will be assessed on day 1 and 14 in the first 2 cycles and then day 1 every 28 days in the 4 subsequent cycles.

Participants will continue treatment for a total duration of 6 cycles or less in case of radiographic or clinical progression as per investigator's judgment or another discontinuation criterion has been met. Participants who complete the study after 6 cycles of treatment may continue to receive abemaciclib (for example, through a patient support program) as per investigators discretion.

4.2. Scientific Rationale for Study Design

The primary objective of the Study JPEC is to characterize the safety of abemaciclib in combination with ET in HR+, HER2- advanced and/or MBC in Indian patients. The number and percentage of patients from the safety population (that is, having received at least one dose of abemaciclib) experiencing a treatment-emergent AE will be summarized per severity grade (as per CTCAE criteria version 5.0) and the number of participants with SAEs and or AESI will be described.

The study is designed to enroll approximately 200 patients in India targeting the same patient populations as were enrolled in the Phase 3 global studies of MONARCH 3 and MONARCH 2.

- Cohort A: patients (similar to MONARCH 3), who are starting initial ET in the advanced/metastatic setting, will be assigned to abemaciclib + anastrozole or letrozole.
- Cohorts B: patients (similar to MONARCH 2), who have received prior ET in the advanced/metastatic setting or relapsed while on or within 1 year after ET in the adjuvant setting, will be assigned to abemaciclib plus fulvestrant.

Patients will remain on study for a maximum of 6 cycles. The final analyses of primary and secondary objectives will be conducted when the last patient comes off study treatment, which is approximately 6 months after the last patient enrolls. This timeframe will enable to

gather sufficient data to characterize the safety of abemaciclib in combination with ET in HR+, HER2- advanced and/or MBC patients enrolled in India.

4.3. Justification for Dose

Clinical trials MONARCH 2 and MONARCH 3 demonstrated efficacy with an acceptable risk- benefit profile when abemaciclib was dosed at 150 mg as combination therapy. Further justification for dose may be found in the IB, Patient Information Leaflet, and Prescribing Information.

Justification for the dosing of approved NSAIs, anastrozole and letrozole, and fulvestrant may be found in the respective Patient Information Leaflet and Prescribing Information. Study JPEC will explore the safety of abemaciclib at a dose of 150 mg twice daily (BD) in combination with ET in Indian patients with HR+, HER2- advanced and/or MBC.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the trial.

5. Study Population

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

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

    - to fulfill the requirement of HR+ disease, a breast cancer must express, by immunohistochemistry (IHC), at least 1 of the hormone receptors (ER or progesterone receptor) as defined in the relevant American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines (Hammond et al. 2010).
    - to fulfill the requirement of HER2- disease, a breast cancer must not demonstrate, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 by either IHC or in-situ hybridization as defined in the relevant ASCO/CAP Guidelines (Wolff et al. 2014). Although not required as a protocol procedure, a patient with a new metastatic lesion should be considered for biopsy whenever possible to reassess HER2 status prior to study entry if clinically indicated.

2. meet either inclusion criterion (2a) or inclusion criterion (2b). Participants meeting inclusion criterion 2a will be enrolled in cohort A and participants meeting inclusion criterion 2b will be enrolled in cohort B.

    (2a) have <u>locoregionally recurrent disease</u> not amenable to resection or radiation therapy with curative intent or <u>metastatic disease</u>

    - relapsed with radiologic evidence of progression more than 1 year from completion of/or with no adjuvant ET

      and

      have received no prior ET for locoregionally recurrent or metastatic disease

      (Note: prior neoadjuvant or adjuvant ET for localized disease may have included, but is not limited to, anti-estrogens or aromatase inhibitors. In addition, a patient may be enrolled if she has received ≤2 weeks of NSAI in this disease setting immediately preceding screening and agrees to discontinue NSAI until study treatment initiation.)

    OR

    - presented de novo MBC and not received any prior ET

(2b) have <u>locoregionally recurrent disease</u> not amenable to resection or radiation therapy with curative intent or <u>metastatic disease</u>

- relapsed with radiologic evidence of progression while receiving neoadjuvant or adjuvant ET, with no subsequent ET received following progression

OR

- relapsed with radiologic evidence of progression within 1 year from completion of adjuvant ET, with no subsequent ET received following progression

OR

- relapsed with radiologic evidence of progression more than 1 year from completion of adjuvant ET and then subsequently relapsed with radiologic evidence of progression after receiving treatment with either an antiestrogen or an aromatase inhibitor as first-line ET for metastatic disease. Participants may not have received more than 1 line of ET or any prior chemotherapy for metastatic disease

OR

- presented de novo with metastatic disease and then relapsed with radiologic evidence of progression after receiving treatment with either an antiestrogen or an aromatase inhibitor as first-line ET for metastatic disease. Participants may not have received more than 1 line of ET or any prior chemotherapy for metastatic disease

3. have postmenopausal status due to either surgical/natural menopause or ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a gonadotropin- releasing hormone (GnRH) agonist such as goserelin. Postmenopausal status due to surgical/natural menopause requires at least 1 of the following:
    - prior bilateral oophorectomy
    - age ≥55 years
    - age <55 years and amenorrhoeic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and follicle-stimulating hormone (FSH) and estradiol levels in the postmenopausal range
4. if postmenopausal status is due to ovarian suppression with a GnRH agonist such as goserelin (initiated at least 28 days prior to Cycle 1 Day 1), participants must have a negative serum pregnancy test at baseline (within 14 days prior to enrollment) and agree to use medically approved precautions to prevent pregnancy during the study and for 3 weeks following the last dose of abemaciclib.

5. sexually active participants, who are of child-bearing potential, must agree to use a medically approved contraceptive method during the study and for at least 3 weeks following the last dose of abemaciclib (for example, intrauterine device, nonhormonal birth control pills, or barrier method).
6. Please refer to Appendix 4 (Section 10.4) for additional reproductive and contraceptive guidance.
7. are female and >18 years of age.
8. have given signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol prior to any study-specific procedures
9. must have adequate organ function, as defined below:

Hematologic System	
Parameter	**Laboratory Value**
ANC	$\geq 1.5\times10^9$/L
Platelets	$\geq 100\times10^9$/L
Hemoglobin	≥9 g/dL
Note: Transfusions to increase a participant's hemoglobin level or initiation of erythropoietin or granulocyte-colony stimulating factor (G-CSF) therapy to meet enrollment criteria is not allowed in the 14 days preceding the first dose of study intervention. If a participant receives transfusions, erythropoietin, or G-CSF therapy ≥14 days prior to the first dose of study intervention, the hematologic criteria listed above must be met following the 14-day window and prior to the first dose of study intervention.	
Hepatic System	
Parameter	**Laboratory Value**
Total bilirubin	≤1.5×ULN Except participants with a documented history of Gilbert Syndrome who must have a total bilirubin level <2.0×ULN
ALT and AST	≤3×ULN with no tumor involvement **OR** ≤5×ULN if the liver has tumor involvement
Renal System	
Parameter	**Laboratory Value**
Serum creatinine	<1.5×ULN

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

10. have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al. 1982).
11. have discontinued previous therapies for cancer as listed:

Previous Treatment	Length of Time Prior to First Dose of study intervention
Cytotoxic therapies or targeted agents that are small molecule inhibitors	≥21 days or ≥5 half-lives, whichever is shorter
Biologic agents that are large molecules including immunotherapy	≥28 days
Investigational agents	≥28 days. If the agent has a long half-life (for example, >2 weeks), then 3 months or 5 half-lives (whichever is longer) should have passed
Radiotherapy	
Limited-field radiotherapy with palliative intent	≥14 days
Other radiotherapy	≥28 days
Major surgery, excluding biopsy	≥28 days

12. are willing to participate for the duration of the study and to follow study procedures.
13. are able to swallow oral formulation of pharmaceutical product (for example, tablets).

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

14. are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study.
15. have visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis. Visceral crisis is not the mere presence of visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease.
16. have clinical evidence or history of central nervous system metastasis. Screening is not required for enrollment.
17. have received prior treatment with chemotherapy (except for neoadjuvant/adjuvant chemotherapy), fulvestrant, everolimus, or any CDK4&6 inhibitor.
18. have received recent (within 28 days prior to study intervention) live vaccination (for example, yellow fever). Seasonal flu vaccinations that do not contain a live virus are permitted.
19. have a personal history of any of the following conditions: presyncope or syncope of either unexplained or cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest.
20. have serious preexisting medical conditions 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], ILD, 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.

21. have inflammatory breast cancer or a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years.
22. have received an autologous or allogeneic stem-cell transplant
23. have clinically relevant active bacterial or fungal infection, or detectable viral infection (for example, human immunodeficiency virus or viral hepatitis). Screening is not required for enrollment.
24. are pregnant or breastfeeding.

5.3. Lifestyle Considerations

Abemaciclib is a cytochrome P450 (CYP) 3A4 substrate. Participants should refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products while participating in the study due to the effect on CYP3A4.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number. The interval between rescreening should be ≥2 weeks. Individuals may be rescreened a maximum of two times. Each time rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number. Repeating of laboratory testing during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening.

6. Study Intervention

Study intervention is defined as any investigational interventions, marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions Administered

Treatment Regimen	Treatment Period	Dose
Cohort A		
Abemaciclib	28-day cycle	150 mg BD on Days 1-28
Anastrozole or Letrozole	28-day cycle	refer to local PI for dosing information
Cohort B		
Abemaciclib	28-day cycle	150 mg BD on Days 1-28
Fulvestrant	28-day cycle	refer to local PI for dosing information

Abbreviation: BD = twice daily; PI = prescribing information.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and recordmaintenance (that is, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.2.1. Selection and Timing of Doses

A treatment cycle is defined as an interval of 28 days. Abemaciclib will be administered orally BD at approximately the same times each day on Days 1 through 28 of a 28-day cycle (±3 days). Details on treatment administration are described in Section 6.1.

A cycle delay or earlier start due to logistical reasons (for example, due to holiday, weekend, inclement weather, or other unforeseen circumstances), will be permitted for up to a maximum of 7 days (and not be considered a protocol violation). In the event of a visit delay, the participant should continue study intervention if she has adequate drug supply.

Participants may continue to receive study intervention for a total duration of 6 cycles or less in case of disease progression, or any other discontinuation criterion is met (See Section 7).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a non-randomized, open-label study.

Participants will be assigned to abemaciclib plus anastrozole/letrozole (Cohort A) or abemaciclib plus fulvestrant (Cohort B) (see section 5.1). Abemaciclib dispensing will be managed by using the interactive web response system (IWRS).

Site personnel will confirm that they have located the correct study medication packages by entering a confirmation number found on the packages into the IWRS.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The participant must take ≥75% of the planned doses for study intervention in a cycle to be deemed compliant. As outlined in Section 6.7, dose suspensions or delays may occur and will not result in a participant being considered as noncompliant. Participants may be considered significantly noncompliant if they are judged by the investigator to have intentionally or repeatedly taken ≥125% of the planned doses of study intervention in a cycle.

6.5. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

Abemaciclib is extensively metabolized through oxidation by CYP3A. In clinical drug interaction studies, coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure 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).

CYP3A4 inhibitors

Strong inhibitors of CYP3A (given via non-topical routes of administration) should be substituted or avoided if possible (Appendix 6 in Section 10.6). This includes grapefruit or grapefruit juice. If the planned duration of coadministration is <28 days, the investigator may consider suspending abemaciclib. Dose suspensions ≥28 days must be discussed with the Eli Lilly and Company (Lilly)-designated medical monitor.

If coadministration with a strong CYP3A inhibitor is unavoidable, investigators should reduce the dose of abemaciclib by 50 mg. That is, for patients receiving 150 mg twice daily, reduce the dose to 100 mg twice daily. For patients who have already dose reduced to 100 mg twice daily for tolerability, reduce the dose further to 50 mg twice daily.

Upon discontinuation of the strong CYP3A inhibitor, the dose of abemaciclib may be re-escalated to the dose that was used before starting the strong inhibitor after a sufficient washout period (3 to 5 half-lives of the strong CYP3A inhibitor). Re-escalation of the abemaciclib dose requires review and approval from the Lilly-designated medical monitor.

CYP3A4 inducers

Inducers of CYP3A should be substituted or avoided if possible (Appendix 6, Section 10.6). Co-administration with a CYP3A inducer ≥28 days must be discussed with the Lilly-designated medical monitor.

The information in Appendix 6 (Section 10.6) is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

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.

The Eli Lilly and Company (Lilly)-designated medical monitor should be contacted if there are any questions regarding concomitant or prior therapy. No other chemotherapy, immunotherapy, radiotherapy, herbal supplements and/or herbal drugs intended to treat cancer, or experimental drugs will be permitted while participants are receiving study intervention, except as described in Section 6.2.1 and Section 6.6.4.

6.6. Palliative Medicine and Supportive Care

Palliative radiation therapy is permitted after discussion with and agreement of the

Lilly-designated medical monitor for irradiating small areas of painful metastases that cannot be managed adequately using systemic or local analgesics. Abemaciclib should be held while participants are receiving palliative radiation therapy and can be restarted after completion of the therapy as per clinical judgement of the investigator. Any symptomatic

deterioration or clinical disease progression requiring, in the opinion of the investigator, other forms of specific antitumor systemic therapy, will be cause for discontinuation of study intervention.

Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the electronic case report form (eCRF).

If clinically indicated at any time during the study, erythropoietin and packed red blood cell transfusions may be used according to ASCO guidelines (Rizzo et al. 2008). Prophylactic antibiotic treatment should be consistent with ASCO guidelines (Flowers et al. 2013).

All concomitant medications should be recorded throughout the participant's involvement in the study.

6.6.1. Supportive Management for Diarrhea

Participants must receive instructions on the management of diarrhea. Participants should be prescribed antidiarrheal therapy (for example, loperamide) at cycle 1 day 1. Sponsor will provide reimbursement for antidiarrheal therapy according to local laws. In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the participant should initiate antidiarrheal therapy (for example, loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Participants should also be encouraged to drink fluids (that is, 8 to 10 glasses ofclear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with antidiarrheal therapy within 24 hours to at least Grade 1 (per CTCAE version 5.0), abemaciclib should be suspended until diarrhea is resolved to at least Grade 1.
- When abemaciclib treatment recommences, dosing should be adjusted as outlined in Section 6.7.1.

For severe cases of diarrhea, the measurement of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered. If diarrhea is severe (requiring intravenous [IV] hydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones should be considered.

Participants with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be carefully monitored and given IV fluid and electrolyte replacement as clinically indicated. Please refer to Section 6.7 for specific dose-related modifications for diarrhea.

6.6.2. Bisphosphonates and RANK-L Targeted Agents

Participants with bone metastases present on baseline imaging should be appropriately treated with approved bone-modifying agents per investigator's discretion (e.g., bisphosphonates or RANK-L targeted agents) per respective approved labels.

6.6.3. Growth Factors

Participants should receive full supportive care. The use of granulocyte-colony stimulating factor is permitted at the discretion of the investigator based on ASCO (Smith et al. 2015) and European Society for Medical Oncology (Crawford et al. 2009) guidelines. See Section 6.7.1.

6.6.4. Surgery

Participants 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-designated medical monitor.

6.6.4.1. Surgery and/or Radiotherapy for Locoregionally Recurrent Breast Cancer

A participant with locoregionally recurrent breast cancer may receive surgery ± radiotherapy if study intervention renders the tumor operable. However, such a participant should not receive study intervention for the period beginning at least 7 days prior to surgery and continuing as clinically indicated after completion of surgery ± radiotherapy to allow for tissue healing and recovery. There is no restriction on the duration of this period without study intervention and, after this period ends, study intervention may resume. Importantly, a participant who receives surgery ± radiotherapy for locoregionally recurrent breast cancer is not considered noncompliant and does not incur a protocol deviation.

6.7. Dose Modification

Dose reductions for abemaciclib should be performed as shown in the table below. Abemaciclib must be reduced sequentially by 1 dose level, unless an exception is granted in consultation with the Lilly-designated medical monitor. For participants requiring a dose reduction of study intervention, any reescalation to a prior dose level is permitted only after

consultation with and approval by the Lilly-designated medical monitor. If a patient receiving the 50-mg BD dose of abemaciclib requires further dose reduction, the patient must be discontinued from abemaciclib. In the event that abemaciclib must be discontinued, a patient may continue to receive ET in the absence of progression per the investigator's clinical judgment.

Abemaciclib dose modification for adverse reactions

Dose Level	Abemaciclib dose
Starting dose	150 mg BID
First dose reduction	100 mg BID
Second dose reduction	50 mg BID
Third dose reduction	Not applicable

Abbreviation: BID = twice daily.

The toxicity dose adjustments and delays of abemaciclib in the tables below are guidance for management of treatment-emergent, related (that is, with reasonable causal relationship with abemaciclib), and clinically significant AEs of abemaciclib. Treatment-emergent laboratory abnormalities of neutrophil count decreased and/or ALT/AST increased, regardless of clinical significance, must follow the dose adjustment table below.

An investigator may suspend or reduce doses without 1 of the criteria below being met and would not be considered a protocol deviation.

Abemaciclib Dose Modification And Management- Hematologic Toxicities

CTCAE Grade	Abemaciclib dose modifications
Grade 1 or 2	No dose modification is required
Grade 3	Suspend dose until toxicity resolves to ≤Grade 2 Dose reduction is not required.
Grade 3 recurrent or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2 Resume at next lower dose
Patient requires administration of a blood cell growth factor	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2 Resume abemaciclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

Abemaciclib Dose Modification and Management- Diarrhea

At the first sign of loose stools, start treatment with antidiarrheal agents (such as loperamide)	
CTCAE Grade[1]	**Abemaciclib dose modifications**
Grade 1	No dose modification is required
Grade 2	If toxicity does not resolve within 24 hours to ≤ Grade 1, suspend dose until resolution No dose reduction is required
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to ≤Grade 1. Resume at next lower dose
Grade 3 or 4 or requires hospitalization	

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

[1] For grading of diarrhea events please refer to Appendix 7 (Section 10.7)

Abemaciclib Dose Modification and Management- Increased ALT/AST

Monitor ALT/AST prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade[1]	**Abemaciclib dose modifications**
Grade 1 Grade 2	No dose modification is required
Persistent or Recurrent Grade 2, or Grade 3	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose
≥Grade 2 (with total bilirubin >2×ULN, in the absence of cholestasis	Discontinue abemaciclib
Grade 4	Discontinue abemaciclib

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

[1] For grading of ALT and AST increased please refer to Appendix 7 (Section 10.7)

Abemaciclib Dose Modification And Management– Interstitial Lung Disease/Pneumonitis

CTCAE Grade[1]	Abemaciclib dose modifications
Grade 1 or 2	No dose modification is required
Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days	Suspend dose until toxicity resolves to baseline or Grade ≤1 Resume at next lower dose.
Grade 3 or 4	Discontinue abemaciclib

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

[1] For grading of pneumonitis events please refer to Appendix 7 (Section 10.7)

Abemaciclib Dose Modification And Management – Venous Thromboembolic Events

CTCAE Grade	Abemaciclib dose modifications
Grade 1 or 2	No dose modification is required
Grade 3 or 4	Suspend dose and treat as clinically indicated. Abemaciclib may be resumed when the patient is clinically stable.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

Abemaciclib Dose Modification And Management – Nonhematologic Toxicities Excluding Diarrhea, ALT/AST Increased, ILD/pneumonitis, and Venous Thromboembolic Events

CTCAE Grade	Abemaciclib dose modifications
Grade 1 or 2	No dose modification is required
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1
Grade 3 or 4	Resume at next lower dose

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ILD = interstitial lung disease.

6.7.1. Dose Suspension and Cycle Delay

Study interventions may be suspended for a maximum of 28 days to allow a patient sufficient time for recovery from study treatment-related toxicity. In exceptional circumstances, a delay >28 days is permitted upon agreement between the investigator and the Lilly- designated medical monitor.

For dose suspensions for abemaciclib related to surgery or palliative radiation see section 6.6.

A delay of a cycle due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation. In exceptional circumstances, a delay >7 days is permitted upon agreement between the investigator and the Lilly-designated medical monitor.

6.7.2. Anastrozole and Letrozole Dose Modification

Dose adjustment for anastrozole and letrozole will be determined by the investigator in accordance with the local Prescribing information. Participants should remain on the same NSAI throughout the study. In exceptional cases, in the absence of evidence of progressive disease, the investigator may discuss a change in NSAI with the Lilly-designated medical monitor. In the event that anastrozole or letrozole are discontinued, the participant may continue abemaciclib alone in the absence of evidence of progression and per the investigator's clinical judgement.

6.7.3. Fulvestrant Dose Modification

Dose adjustment for fulvestrant will be determined by the investigator in accordance with the Prescribing Information. In the event that fulvestrant is discontinued, the participant may continue abemaciclib alone, in the absence of evidence of progression, and per the investigator's clinical judgement.

6.8. Intervention after the End of the Study

Please refer to the study schema (Section 1.2) for a depiction of study completion and the end of study.

6.8.1. Study Completion

Study completion will occur following the final analysis of primary and secondary objectives, which will be conducted when the last patient completed 6 cycles of study intervention and comes off the study. This is expected approximately 6 months after the last patient entered treatment.

The end of study definition is defined in Section 4.4. Investigators will continue to follow the SoA provided in Section 1.3 until notified by Sponsor that end of study has occurred.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Participants may discontinue the study intervention at any time for any reason.

The reason and date of discontinuation must be collected for all participants and documented on the corresponding CRF.

Participants will be discontinued from study intervention in the following circumstances:

- participant completed 6 cycles of study intervention
- participant decision
  - the participant or the participant's designee (for example, parents or legal guardian) requests to be discontinued from study intervention
- 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)
- investigator decision
  - the investigator decides that the patient should be discontinued from the study or study intervention
  - if the participant, for any reason, requires treatment from another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study intervention will occur prior to introduction of the new agent.
  - the participant is significantly noncompliant with study procedures and/or intervention.
- the participant is enrolled in any other clinical trial involving an investigational product or other type of medical research judged not to be scientifically or medically compatible with this study
- radiographic or symptomatic disease progression as per investigator judgment
- the participant experiences unacceptable toxicity
- the patient becomes pregnant during the study

7.2. Participant Discontinuation/Withdrawal from the Study

Participants 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 participant requests to be withdrawn from the study
- the participant completed 6 cycles of study intervention and/or completed the short-term follow-up visit
- the study has been completed as defined in Section 6.8.1.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment.

If the investigator and the sponsor clinical research physician (CRP)/clinical research scientist (CRS) agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP/CRS to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 1.3 (SoA), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

7.3. Lost to Follow up

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

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3). For each patient, vital signs, laboratory tests, and other tests should be collected as shown in the SoA (Section 1.3).

Results from any clinical laboratory test analyzed by a central laboratory (refer to Appendix 2, Section 10.2) will be provided to investigator sites by Lilly or its designee.

Refer to Section 8.3 for details on the recording of AEs.

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods. Additional information regarding guidance for monitoring of hepatic function, renal function, VTE, and ILD/pneumonitis can be found in sections 8.2.2.

8.2.1. Clinical Safety Laboratory Assessments

Lilly or its designee will provide the investigator with the results of safety laboratory tests analyzed by a central vendor.

See Appendix 2 (Section 10.2), for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within Visit 801 after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE, AE, or dose modification), then the results must be recorded in the CRF.

8.2.2. Safety Monitoring

8.2.2.1. Hepatic Safety Monitoring

Close Hepatic Monitoring And Evaluation

Liver testing (Section 10.5, Appendix 5), including ALT, AST, alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin (D. Bil), gamma-glutamyl transferase (GGT), and creatine kinase (CK), should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of …	develops the following elevations:
ALT or AST <1.5×ULN	ALT or AST ≥5×ULN or ALT or AST ≥3x ULN concurrent with TBL ≥2×ULN
ALT or AST ≥1.5×ULN	ALT or AST ≥3×baseline or ALT or AST ≥2×baseline concurrent with TBL ≥2×ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses

(for example, heart failure, systemic infection, hypotension, or seizures), history of concomitant medications (including over-the-counter, herbal and dietary supplements, history of alcohol drinking, and other substance abuse). In addition, the evaluation should include a blood test for prothrombin time (PT)-INR; serological tests for viral hepatitis A, B, C, E, autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computed tomography [CT] scan).

Based on the patient's history and initial evaluation results, further testing should be considered, in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, and/or a liver biopsy.

Additional Hepatic Safety Data Collection

Additional safety data should be collected via the eCRF, if 1 or more of the following conditions occur:

In participants enrolled with baseline ALT or AST<1.5 ULN

- Elevation of serum ALT or AST to ≥5×ULN on 2 or more consecutive blood tests
- The combination of elevated ALT or AST ≥3×ULN and elevated TBL ≥2×ULN

In participants enrolled with baseline ALT or AST ≥1.5×ULN

- Elevated ALT or AST ≥3×baseline on 2 or more consecutive tests
- The combination of elevated ALT or AST ≥2×baseline and elevated TBL ≥2×ULN

In all study participants

- Discontinuation from study treatment due to a hepatic event or abnormality of liver tests
- Occurrence of a hepatic event considered to be a SAE

8.2.2.2. Venous Thromboembolic Events (VTEs)

VTE has been identified as an adverse drug reaction for abemaciclib in combination with endocrine therapy. In the randomized Phase 3 studies in participants with breast cancer treated with abemaciclib in combination with ET, a greater number of participants experienced VTEs in the abemaciclib plus ET arm than in the placebo plus ET arm or ET alone arm. The majority of participants who experienced VTEs were treated with anticoagulants.

At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. Participants should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate. Additional information is available in the IB.

8.2.2.3. Serum Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting glomerular filtration rate (as measured by iohexol clearance). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing (remained elevated but stable through the treatment period) were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen, cystatin C, or calculated glomerular filtration rate based on cystatin C.

Dose adjustment (omission, reduction, or discontinuation) should not be based solely 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, a cystatin C measurement may be performed to confirm renal status. Dose alteration should follow the protocol guidance for nonhematological toxicities (Section 6.7).

8.2.2.4. Interstitial Lung Disease/Pneumonitis

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

Ask your participants to report any new or worsening pulmonary symptoms such as dyspnea, cough, and 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, bronchoalveolar lavage, and biopsy as clinically indicated.

Refer to Section 6.7 for guidance on dose adjustments of abemaciclib for participants with ILD/pneumonitis. Discontinue abemaciclib in cases of severe (Grade 3 or 4) ILD/pneumonitis.

8.2.3. Safety Surveillance

The sponsor has robust safety surveillance processes based on recommendation made by Council for International Organizations of Medical Sciences (CIOMS) Working Group VI - Management of Safety Information from Clinical Trials Report. These processes are in line with FDA's expectations for Safety Assessment Committees and the European Medical Agency expectations for monitoring safety in clinical trials.

Each investigational drug has a Developmental Safety Surveillance Team (DSST) which is responsible for monitoring the safety of participants and overseeing the evolving safety

profile of investigational drugs. The DSST will review all available data including but not limited to clinical trial data (cumulative AE and SAE data and laboratory data), non-clinical data (toxicology studies), epidemiology studies and literature. The team will conduct real time review of all SAEs and other incoming expedited safety reports. The DSST is also responsible for review of accumulating safety data across all trials for the investigational drug. The DSST will meet in a timely manner at predefined intervals or on an ad-hoc basis as required.

The DSST is a multidisciplinary team which includes a physician/scientist who are well versed in Pharmacovigilance and with the therapeutic area for which the investigational drug is being developed. The roles and responsibilities of this team and the processes are clearly defined in Lilly's internal Standard Operating Procedures.

Each investigational drug has a Developmental Safety Management Team (DSMT) which is a cross-functional, multidisciplinary team and includes DSST members, study team physicians and other members depending on the necessity such as epidemiologist, clinical pharmacologist, toxicologist, statistician. The DSST and DSMT work together to review clinical data from the clinical trial.

The DSST can make recommendations to the DSMT in order to minimize risk to participants in clinical trials. Such recommendations will include (but are not limited to) changes to conduct of the trial, determination of new adverse drug reactions and determining if event(s) meets the criteria for expedited reporting to regulators (such as investigational new drug safety reports) and investigators.

In addition, each individual clinical trial study team has clearly defined processes to review all relevant safety data at cohort level and trial level in order to monitor safety of participants in clinical trials and enable trial level decisions such as dose escalation. More information about these processes can be found in Section 6.7 of the protocol.

Lilly Global Patient Safety has a robust process, for expedited communication of SAEs and suspected unexpected serious adverse reactions per regulatory requirements and other important study information as needed. The protocol gives detailed information to study sites for collection and reporting of AEs and SAEs (see Section 8.3 and Appendix 3 [Section 10.3]).

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until participation in study has ended. All AEs will be collected from the signing of the ICF or until end of study visit.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the AE CRF.

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to sponsor begins after the patient has signed the ICF and has received study intervention. However, if an SAE occurs after signing the ICF, but prior to receiving abemaciclib, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Participant Diary

A diary will be provided to participants in order to help track treatment compliance and for the participant to record possible side effects experienced during the treatment cycle. The investigator or designee should review the diary for completion and discuss any reported side effect with the patient.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safetyof a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

The patient population in Study JPEC is restricted to post-menopausal women so pregnancies are therefore highly unlikely to occur in this study.

However, if a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3 (Section 10.3).

Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

More information about the AESI for abemaciclib can be found in the IB.

8.3.7. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a trial intervention.

The Sponsor 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 to facilitate process and product improvements.

Participants 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.

NOTE: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.3 and Appendix 3 (Section 10.3) of the protocol.

8.4. Treatment of Overdose

In the event of an overdose, the investigator should:

1. Contact the Lilly-designated medical monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities
3. Document the quantity of the excess dose as well as the duration of the overdose.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Lilly-designated medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

Not applicable.

8.8. Biomarkers

Not applicable.

8.9. Immunogenicity Assessments

Not applicable.

8.10. Medical Resource Utilization and Health Economics

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

No formal statistical hypotheses exist, and no formal statistical hypothesis testing will be performed.

9.2. Sample Size Determination

Approximately 200 participants with ER+, HER2- locally advanced or MBC will be enrolled in this study, with a minimum of at least 50 participants per cohort. The sample size has been selected to allow adequate assessment of study primary objective on safety. It can provide adequate precision for the estimated incidence rate of participants having a specified AE. With a total sample size of N = 200 for the study, example point estimates of incidence rates and corresponding 2-sided 95% CIs are summarized in the table below. The values are provided as a reference for estimation rather than a basis of any decision criteria.

Estimated Incidence Rate and 2-Sided 95% CI

N = 200			
		95% CI[a]	
Number of Cases	Estimated Rate	Lower Limit	Upper Limit
10	0.05	0.02	0.09
20	0.10	0.06	0.15
40	0.20	0.15	0.26
60	0.30	0.24	0.37
80	0.40	0.33	0.47
120	0.60	0.53	0.67
140	0.70	0.63	0.76
160	0.80	0.74	0.85
180	0.90	0.85	0.94

Abbreviations: CI = confidence interval; N = number of participants.

[a] 95% Clopper-Pearson interval for binomial distribution.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who sign the informed consent form.
Safety	All participants assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.

9.4. Statistical Analyses

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

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 statistical analysis plan and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The statistical analysis plan will be finalized prior to first patient visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. Primary and Secondary Endpoint(s)

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

The Medical Dictionary for Regulatory Activities (MedDRA) Version (25.0x [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 and by decreasing frequency of preferred term within the system organ class.

Safety analyses will include summaries of the following:

- AEs, including severity in CTCAE grade and possible relationship to study intervention
- SAEs, including possible relationship to study intervention
- Discontinuations from study treatment due to AEs

Time to treatment discontinuation is defined as the time from first dose until the date of treatment discontinuation.

9.4.2. Other Analyses

9.4.2.1. Patient Disposition

A detailed description of patient disposition will be provided, including a summary of the number and percentage of participants entered into the study, and treated in the study, or discontinuing (overall and by reason for discontinuation). A summary of all the important protocol deviations will be provided.

9.4.2.2. Patient Characteristics

A summary of baseline patient and disease characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported using descriptive statistics.

9.4.2.3. Concomitant Therapy

A summary of prior and concomitant medications will be reported.

9.4.2.4. Treatment Compliance

Fulvestrant will be administered at the investigator site; therefore, treatment compliance is assured.

Study treatment compliance for other study treatments will be assessed as the proportion of treatment that is actually taken, relative to what is expected, after accounting for protocol-defined dose adjustments. Study treatment taken will be derived from the difference between the total number of pills dispensed and returned over the course of the patient's treatment.

9.5. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs [and/or UADEs] or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The Sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.4. Committees Structure

Not applicable.

10.1.5. Dissemination of Clinical Study Data

Dissemination of study data will be performed according to all applicable Lilly policies.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and assures appropriate participant therapy and/or follow-up.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (fore example, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture system will be stored at third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Sponsor data warehouse.

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

10.1.9. Publication Policy

In accordance with the sponsor's publication policy the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.10. Investigator Information

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed as indicated in the table.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.

Investigators must document their review of each laboratory safety report. Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Clinical Laboratory Tests

Hematology -Central Laboratory	
Basophils	Lymphocytes
Eosinophils	Mean cell hemoglobin concentration (MCHC)
Erythrocytes (RBC)	Mean cell volume (MCV)
Hemoglobin (HGB)	Monocytes
Hematocrit (HCT)	Neutrophils
Leukocytes (WBC)	Platelets (PLT)

Clinical Chemistry - Central Laboratory	
Serum concentrations of:	
Alanine aminotransferase (ALT)	Chloride
Albumin	Creatinine
Alkaline phosphatase (ALP)	Cystatin C
Aspartate aminotransferase (AST)	Potassium
Bilirubin, total	Protein, total
Bilirubin, direct	Sodium
Blood urea nitrogen (BUN) or blood urea Calcium	

Pregnancy Test (Only for Participants Receiving Ovarian Suppression with a GnRH Agonist) **– Local Laboratory**

Serum pregnancy test

Postmenopausal Confirmation Testing (Required only for women <55 years with amenorrhea for at least 12 months to confirm post-menopausal status) **- Local Laboratory**

Follicle-stimulating hormone (FSH)	Estradiol

Note: 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 added together and reported on the CRF, unless the CRF specifically provides an entry field for bands.

Abbreviations: CRF = case report form; GnRH = gonadotropin-releasing hormone; RBC = red blood cells; WBC = white blood cells.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, per se, will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy willbe reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess the intensity of each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always assess the causality of every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to Sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Lilly-designated medical monitor by telephone.
- Contacts for SAE reporting can be found in SAE form.

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Lilly-designated medical monitor.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SAE form.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (for example, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female is defined as, women with:
   - 12 months of amenorrhea for women >55, with no need for FSH
   - 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (for example oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective ER modulators (SERMs), or chemotherapy that induced amenorrhea)

Contraception Guidance:

Please follow the contraceptive guidelines below.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Intrauterine device
• Bilateral tubal occlusion
• Vasectomized partner • *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90days.)*
Highly Effective Methods[b] That Are User Dependent
• Sexual abstinence *(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 intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.)*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

Collection of Pregnancy Information

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, including fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at >20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with participants in consultation with the Lilly-designated medical monitor.

Hepatic Evaluation Testing – Refer to protocol Hepatic Safety Monitoring Section 8.2.2.1 for guidance on appropriate test selection.

- **For testing selected, analysis is required to be completed by the Lilly designated central laboratory except for microbiology.**
- **Local testing may be performed in addition to central testing when required for immediate patient management.**
- **Results will be reported if a validated test or calculation is available.**

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - Red Blood Cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - White Blood Cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen Protein Adducts
Platelets	Alkaline Phosphatase Isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	Ethyl Alcohol (EtOH)
Prothrombin Time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin A (IgA [Quantitative])
Hepatitis A Virus (HAV) Testing:	Immunoglobulin G (IgG [Quantitative])
HAV Total Antibody	Immunoglobulin M (IgM [Quantitative])
HAV IgM Antibody	Phosphatidylethanol (PEth)
Hepatis B Virus (HBV) Testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug Screen
Hepatitis B surface antibody (Anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (Anti-HBc)	**Other Serology**

Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA)[a]
HBV DNA[d]	Anti-actin antibody[b]
Hepatis C Virus (HCV) Testing:	Epstein-Barr Virus (EBV) Testing:
HCV antibody	EBV antibody
HCV RNA[d]	EBV DNA[d]
Hepatitis D Virus (HDV) Testing:	Cytomegalovirus (CMV) Testing:
HDV antibody	CMV antibody
Hepatitis E Virus (HEV) Testing:	CMV DNA[d]
HEV IgG antibody	Herpes Simplex Virus (HSV) Testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[d]	HSV (Type 1 and 2) DNA[d]
Microbiology[c]	Liver Kidney Microsomal Type 1 (LKM-1) Antibody
Culture:	
Blood	
Urine	

Abbreviations: CRF = case report form; DNA = deoxyribonucleic acid; Ig = immunoglobulin; INR = international normalized ratio; RNA = ribonucleic acid.

[a] This is not required if Anti-Actin Antibody is tested.

[b] This is not required if Anti-smooth muscle antibody (ASMA) is tested.

[c] Assayed by Investigator-designated local laboratory ONLY. For some abnormal lab values, only the related diagnosis will be reported in the CRF.

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

10.6. Appendix 6: 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[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine Rifampin
Rifabutin
St John's wort

Moderate Inducers of CYP3A
Bosentan
Lesinurad
Modafinil
Primidone
Telotristatethyl

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

[a] Important note: All participants may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated.

Abbreviation: CYP = cytochrome P450.

10.7. Appendix 7: CTCAE 5.0 Diarrhea/Pneumonitis/ALT and AST Increased Definitions

Diarrhea/Pneumonitis/ALT and AST increased will be evaluated in this study using the criteria proposed by CTCAE v5.0 revised: Gastrointestinal disorders, Respiratory, Thoracic and Mediastinal Disorders.

Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
Gastrointestinal Disorders					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of ≥7 stools per day over baseline; 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 an increase in frequency and/or loose watery bowel movements					
Respiratory, Thoracic, and Mediastinal Disorders					
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 (for example, tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					

Abbreviation: ADL = activities of daily living.

Investigations					
Alanine aminotransferase (ALT) increased	>ULN through 3.0 x ULN if baseline was normal; 1.5 through 3.0 x baseline if baseline was abnormal	>3.0 through 5.0 x ULN if baseline was normal; >3.0 through 5.0 x baseline if baseline was abnormal	>5.0 through 20.0 x ULN if baseline was normal; >5.0 through 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Death
Definition: a finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					

Aspartate aminotransferase (AST) increased	>ULN through 3.0 x ULN if baseline was normal; 1.5 through 3.0 x baseline if baseline was abnormal	>3.0 through 5.0 x ULN if baseline was normal; >3.0 through 5.0 x baseline if baseline was abnormal	>5.0 through 20.0 x ULN if baseline was normal; >5.0 through 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Death
Definition: a finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					

Abbreviation: ADL = activities of daily living; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; ULN = upper limit of normal.

10.8 Appendix 8: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of This Appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional Circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing Changes Under Exceptional Circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

Ethical review boards, regulatory bodies, and any other relevant local authorities, as required, will be notified as early as possible to communicate implementation of changes in study conduct due to exceptional circumstances. To protect the safety of study participants, urgent changes may be implemented before such communications are made, but all changes will be reported as soon as possible following implementation. If approval of ERBs, regulatory bodies, or both is required per local regulations, confirmation of this approval will be retained in the study records.

In the event written approval is granted by the sponsor for changes in study conduct, additional written guidance, if needed, will be provided by the sponsor.

Considerations for Making a Change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed Consent

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote visits,"
- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct During Exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

1. **Remote visits**

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments.
Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures on the SoA may be performed at such visits.
Other alternative locations: Other procedures may be done at an alternate location in exceptional circumstances.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged. Furthermore, every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

2. **Local laboratory testing option**

Local laboratory testing may be conducted in lieu of central laboratory testing with sponsor approval. However, central laboratory testing must be retained whenever possible for all visits where central laboratory testing is required. The local laboratory must be qualified in accordance with applicable local regulations.

3. **Study intervention and ancillary supplies (including participant diaries)**

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, and
- arranging delivery of study supplies

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

4. Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening visit(s) are valid for a maximum of 28 days as outlined in the study protocol. The following rules will be applied for active, nonrandomized participants who have signed informed consent and are undergoing screening procedures but whose participation in the study must be paused due to exceptional circumstances:

- If the screening period lasts for more than 42 days due to exceptional circumstances: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual SoA should be followed, starting at screening visit(s) to ensure participant eligibility by Cycle 1 Day 1.

5. Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should follow the visit windows described in the SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance and approval from the sponsor. This minimizes missing data and preserves the intended conduct of the study.
For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.
- Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.9 Appendix 9: Abbreviations

Term	Definition
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BCT	breast conservation treatment
CAP	College of American Pathologists
CDK	cyclin-dependent kinase
CDK 4&6	cyclin-dependent kinases 4 & 6
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRS	clinical research scientist
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome p450
DSMT	Developmental Safety Management Team
DSST	Developmental Safety Surveillance Team

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ER	estrogen receptor
ET	endocrine therapy
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
HER2-	human epidermal growth factor receptor 2 negative
HR+	hormone receptor positive
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IHC	immunohistochemistry
ILD	Interstitial lung disease
Interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on 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 Boards
IV	intravenous
IWRS	interactive web response system
MBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
NSAIs	nonsteroidal aromatase inhibitors
ORR	objective response rate
OS	overall survival
Participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PFS	progression-free survival
Rb	retinoblastoma
SAE	serious adverse event
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
SoA	schedule of activities
ULN	upper limit of normal
VTE	venous thromboembolic events

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