I3Y-MC-JPCU Protocol (b)

A Multicenter, Open-Label, Randomized-Controlled Study of Abemaciclib, a CDK4 and 6 Inhibitor, in Combination with Fulvestrant Compared to Chemotherapy in Women with HR Positive, HER2 Negative Metastatic Breast Cancer with Visceral Metastases

NCT04031885

Approval Date: 20-Feb-2020

Title Page

Protocol Title: A Multicenter, Open-Label, Randomized-Controlled Study of Abemaciclib, a CDK4 and 6 Inhibitor, in Combination with Fulvestrant Compared to Chemotherapy in Women with HR Positive, HER2 Negative Metastatic Breast Cancer with Visceral Metastases

Protocol Number: I3Y-MC-JPCU

Amendment Number: (b)

Compound Number: LY2835219

Study Phase: 4

Short Title: A Study of Abemaciclib in Combination with Fulvestrant Compared to Chemotherapy in Women with HR+, HER2- Metastatic Breast Cancer with Visceral Metastases

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

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

Approval Date: 20-Feb-2020 GMT

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment a	21-Jun-2019
Protocol I3Y-MC-JPCU	15-Apr-2019

Amendment b

Overall Rationale for the Amendment:
This amendment incorporates updates made in the development core safety information of the Investigator's Brochure. Additional protocol changes and rationale are provided below.

Section # and Name	Description of Change	Brief Rationale
6.6.1 Abemaciclib	Updated and added new abemaciclib dose modification and management tables and language.	Alignment with Investigator's Brochure update.
8.2.1.4 Interstitial Lung Disease (ILD)/Pneumonitis	Revised language.	Alignment with Investigator's Brochure update.
8.2.1.1 Hepatic Safety Monitoring	Deleted and replaced with new hepatic safety monitoring language.	Changes to the Special Hepatic Safety Data Collection were done to ensure a comprehensive evaluation of patients with treatment-emergent abnormal liver tests and to align with current guidance from the Lilly Liver and Gastrointestinal (GI) Safety Advisory Committee.

Section # and Name	Description of Change	Brief Rationale
Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments	Deleted and replaced with new hepatic safety monitoring language. Added: Cell morphology (RBC and WBC), HBV DNA, HCV RNA, HDV antibody, HEV RNA, blood culture, urine culture, Acetaminophen, Acetaminophen Protein Adducts, Alkaline Phosphatase Isoenzymes, Ceruloplasmin, Copper, Ethyl Alcohol (EtOH), Immunoglobulin IgA (Quantitative), Immunoglobulin IgG (Quantitative), Immunoglobulin IgM (Quantitative), Phosphatidylethanol (PEth), Drug Screen, Ethyl glucuronide (EtG), EBV antibody, EBV DNA, CMV antibody, CMV DNA, HSV (Type 1 and 2) antibody, HSV (Type 1 and 2) DNA, and Liver Kidney Microsomal Type 1 (LKM-1) Antibody.	Changes to the Special Hepatic Safety Data Collection were done to ensure a comprehensive evaluation of patients with treatment-emergent abnormal liver tests and to align with current guidance from the Lilly Liver and Gastrointestinal (GI) Safety Advisory Committee.
Throughout	Added “at least 6 hours apart” to describe BID dosing.	Clarification.
1.3 Schedule of Activities	Removed grouping of Cycle 1 and 2 and added column for Cycle 2.	No new procedures were added. Revised for readability.
1.3 Schedule of Activities	Changed visit window for Cycle 1 Day 1 to minus 7 days.	Revised for flexibility.
1.3 Schedule of Activities	Clarified clinical tumor measurement assessment timing and added window.	Revised for flexibility and clarificiation.
1.3 Schedule of Activities	Clarified radiologic tumor measurement instructions.	Clarification.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Clarified x-ray, or CT scan with bone windows, or MRI assessment instructions.	Clarification.
1.3 Schedule of Activities	Merged Worst pain NRS, Bowel movement diary, Bristol stool scale, and loperamide doses into one row and added new instructions.	Revised for readability and added instructions for clarity.
1.3 Schedule of Activities	Merged FACT GP5, PRO CTCAE, and EORTC IL36 into one row and added new instructions.	Revised for readability and added instructions for clarity.
1.3 Schedule of Activities; 6.3 Measures to Minimize Bias: Randomization and Blinding	Added abemaciclib, fulvestrant, and chemotherapy administration window from randomization to C1D1.	Revised to allow flexibility.
5.1 Inclusion Criteria	Added omentum as an example in Inclusion Criterion 8.	Revised to add an example.
5.2 Exclusion Criteria	Merged Exclusion Criterion 26 into Exclusion Criterion 23.	Revised for readability.
5.2 Exclusion Criteria	Changed “randomization” to “C1D1” in Exclusion Criterion 28.	Clarified timing of biophosphonates initiation.
6.5 Concomitant Therapy	Removed cautionary language regarding coadministration of narrow therapeutic index CYP substrate drugs	Alignment with Investigator’s Brochure update.
8.1 Efficacy Assessments	Changed “bone scans” to “bone scintigraphy”	Clarification and alignment with Schedule of Activities.
9.4.4.1 Patient-Reported Outcome (PRO)	Changed PRO summary to visit and treatment arm, overall treatment arm, and overall for the trial.	Alignment with Schedule of Activities.
10.6 Appendix 6: CTCAE 5.0 Diarrhea/Pneumonitis Definition	Added pneumonitis CTCAE definition.	Reference for investigators.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and formatting changes	Minor and therefore not summarized.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Multicenter, Open-Label, Randomized-Controlled Study of Abemaciclib, a CDK4 and 6 inhibitor, in Combination with Fulvestrant Compared to Chemotherapy in Women with HR Positive, HER2 Negative Metastatic Breast Cancer with Visceral Metastases

Short Title:

A Study of Abemaciclib in Combination with Fulvestrant Compared to Chemotherapy in Women with HR+, HER2- Metastatic Breast Cancer with Visceral Metastases

Rationale:
The use of cytotoxic chemotherapy may be initiated earlier in the course of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer (MBC) than recommended by the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines, potentially denying patients an effective and tolerable standard of care (SOC) regimen containing endocrine therapy (ET).

The proposed Study I3Y-MC-JPCU (hereafter referred to as Study JPCU) will compare the efficacy of abemaciclib, a cyclin-dependent kinase (CDK) 4 and 6 inhibitor, in combination with fulvestrant to that of physician's choice of chemotherapy (capecitabine, docetaxel, nab-paclitaxel or paclitaxel) in patients with HR+, HER2- MBC with at least 1 site of visceral metastases and at least 1 line of prior ET. Efficacy will be measured by the primary endpoint objective response rate (ORR).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy of abemaciclib in combination with fulvestrant to chemotherapy	• ORR
Secondary	
• To further characterize the efficacy of abemaciclib in combination with fulvestrant compared to chemotherapy	• PFS • TTR • DoR • PFS2
• To compare the safety and tolerability of abemaciclib in combination with fulvestrant to chemotherapy	• Safety: including but not limited to TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE version 5.0

Abbreviations: CTCAE = Common Terminology Criteria in Adverse Events; DoR = duration of response; TTR = time to response; ORR = objective response rate; PFS = progression-free survival; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Overall Design:

Study JPCU is a multicenter, open-label, randomized-controlled study of abemaciclib in combination with fulvestrant compared to physician's choice of chemotherapy in women with HR+, HER2- locally advanced or metastatic breast cancer (hereafter referred to as "metastatic breast cancer") who have poor prognosis due to visceral metastases.

Disclosure Statement:

This is a parallel group treatment study with 2 arms and no masking.

Number of Patients:

Approximately 300 patients will be randomized in the study.

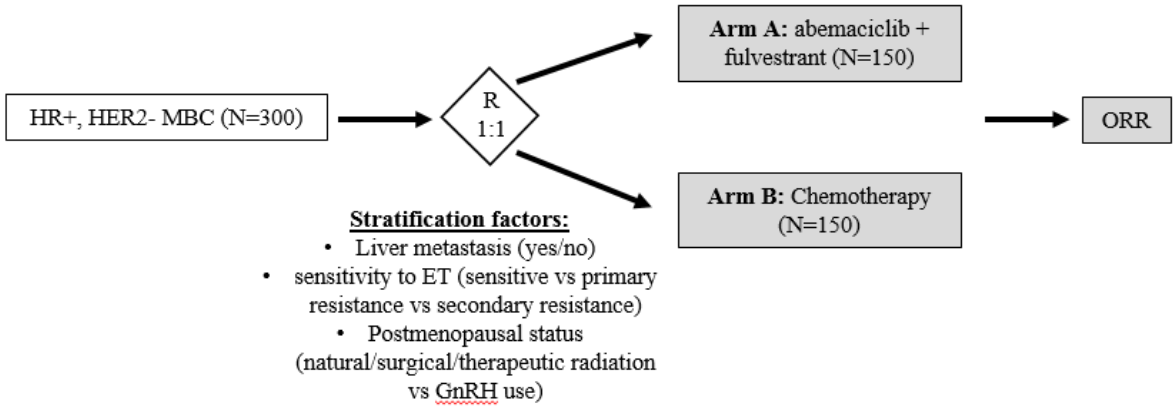
Intervention Groups and Duration:

Arm	Arm A		Arm B
Intervention	Abemaciclib	Fulvestrant	Chemotherapy (capecitabine, docetaxel, nab-paclitaxel, or paclitaxel)
Dose	150 mg	500mg	Refer to PI or per physician's routine clinical practice
Schedule	BID	C1D1,C1D15, Day 1 of each subsequent cycle	Refer to PI or per physician's routine clinical practice
Route	PO	IM	Refer to PI

Abbreviations: BID = twice a day, at least 6 hours apart; C = Cycle; D = Day; IM = intramuscular; PI = package insert; PO = by mouth.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: ET = endocrine therapy; GnRH = gonadotropin-releasing hormone; HER2- = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor positive; MBC = metastatic breast cancer; N = number of enrolled patients; ORR = objective response rate; R = randomization.

1.3. Schedule of Activities (SoA)

This section includes the following SoAs:

- Baseline, On-Study, and Post-Study Treatment Follow-Up SoA for all patients
- Continued Access SoA for all patients

Baseline, On-Study and Post-Study Treatment Follow-Up SoA for All Patients

Study Period	Baseline		Study treatment (Cycle = 21 or 28 days)						Post-discontinuation		Instructions
Cycle/Visit	Screening		Cycles 1		Cycle 2		Cycle 3	Cycle 4-n	Short-Term Follow-up[a]	Long-Term Follow-up[b]	
Visit duration for Arm A (days)	Up to 28		28		28		28	28	30	90	
Visit duration for Arm B (days)	Up to 28		21 or 28		21 or 28		21 or 28	21 or 28	30	90	
Relative Day within Dosing Cycle & Visit Window	≤28	≤14	1 (-7d)	15 (±3d)	1 (±3d)	15 (±3d)	1 (±3d)	1 (±3d)	V801 (±7d)	V802-8XX (±14d)	
Procedure											
Informed consent	X										ICF must be signed before any protocol-specific procedures are performed. See Appendix 1.
Inclusion/exclusion criteria		X									See Section 5.
Medical history	X										Includes assessment of pre-existing conditions, historical illnesses, prior anticancer therapy and habits.
Concomitant medication	X		X						X		Record prior and concurrent medications at baseline. Record all premedication, supportive care, and concomitant medication continuously at every visit and throughout the study.
Clinically directed physical examination		X	X		X		X	X	X		
Height, weight and vital signs		X	X		X		X	X	X		Includes height (only at baseline), weight (only at D1 of every cycle), BP, pulse, and temperature.
ECG	X										Collect locally.
ECOG performance status		X	X		X		X	X	X		During study treatment, perform ≤3 days prior to treatment.
AE collection	X		X						X		Collect continuously at every visit and throughout the study. Use CTCAE v 5.0
Tumor Assessments											

Study Period	**Baseline**		**Study treatment (Cycle = 21 or 28 days)**						**Post-discontinuation**		**Instructions**
Cycle/Visit	**Screening**		**Cycles 1**		**Cycle 2**		**Cycle 3**	**Cycle 4-n**	**Short-Term Follow-up[a]**	**Long-Term Follow-up[b]**	
Visit duration for Arm A (days)	Up to 28		28		28		28	28	30	90	
Visit duration for Arm B (days)	Up to 28		21 or 28		21 or 28		21 or 28	21 or 28	30	90	
Relative Day within Dosing Cycle & Visit Window	≤28	≤14	1 (-7d)	15 (±3d)	1 (±3d)	15 (±3d)	1 (±3d)	1 (±3d)	V801 (±7d)	V802-8XX (±14d)	
Procedure											
Clinical Tumor Measurement (lesions that are palpable or visible on exam)	X							See Instructions	See instructions		Assessments should be performed at baseline and Q12W (±7d) from randomization of study therapy. See Section 8.1 for additional guidance.
Radiologic Tumor Measurement (e.g.; CT, MRI)	X						See Instructions		See instructions		• Perform a CT or MRI scan of the chest, abdomen, pelvis and any clinically indicated sites of disease at baseline and every Q12W (±7 days) after randomization until documented disease progression per the RECIST v1.1 criteria, initiation of new anticancer therapy, death, patient withdrawal, or study completion, whichever occurs first. • See Section 8.1 for additional guidance.
Bone scintigraphy	X						See Instructions		See instructions		**Required for all patients at baseline and post-baseline** every Q24W (±7 days), or to confirm complete response, or when progression in bone is suspected until documented disease progression per the RECIST v1.1 criteria, initiation of new anticancer therapy, death, patient withdrawal, or study completion, whichever occurs first See Section 8.1 for additional guidance.

Study Period	Baseline		Study treatment (Cycle = 21 or 28 days)						Post-discontinuation		Instructions
Cycle/Visit	**Screening**		**Cycles 1**		**Cycle 2**		**Cycle 3**	**Cycle 4-n**	**Short-Term Follow-up[a]**	**Long-Term Follow-up[b]**	
Visit duration for Arm A (days)	Up to 28		28		28		28	28	30	90	
Visit duration for Arm B (days)	Up to 28		21 or 28		21 or 28		21 or 28	21 or 28	30	90	
Relative Day within Dosing Cycle & Visit Window	≤28	≤14	1 (-7d)	15 (±3d)	1 (±3d)	15 (±3d)	1 (±3d)	1 (±3d)	V801 (±7d)	V802-8XX (±14d)	
Procedure											
X-ray, or CT scan with bone windows, or MRI	X						See Instructions		See instructions		**Required only for patients with bone disease identified at baseline** Assessment should be performed at baseline and every Q12W (±7 days) after randomization until documented disease progression per the RECIST v1.1 criteria, initiation of new anticancer therapy, death, patient withdrawal, or study completion, whichever occurs first. See Section 8.1 for additional guidance
Clinical laboratory tests											
Pregnancy Test		X									Only for postmenopausal women whose ovarian suppression is due to a GnRH agonist. See Appendix 2.
Postmenopausal Confirmation Testing		X									Only for postmenopausal women <60 years, and ammehoric for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression). See Appendix 2.
Hematology		X	X	X	X	X	X		X		See Appendix 2.
Coagulation		X									See Appendix 2. For patients receiving oral coumarin-derivative anticoagulations while on chemotherapy, coagulation should be collected locally at every visit.
Urinalysis		X									See Appendix 2.
Clinical Chemistry		X	X	X	X	X	X	X	X		See Appendix 2.
Post-study collection											

Study Period	Baseline		Study treatment (Cycle = 21 or 28 days)						Post-discontinuation		Instructions
Cycle/Visit	**Screening**		**Cycles 1**		**Cycle 2**		**Cycle 3**	**Cycle 4-n**	**Short-Term Follow-up[a]**	**Long-Term Follow-up[b]**	
Visit duration for Arm A (days)	Up to 28		28		28		28	28	30	90	
Visit duration for Arm B (days)	Up to 28		21 or 28		21 or 28		21 or 28	21 or 28	30	90	
Relative Day within Dosing Cycle & Visit Window	≤28	≤14	1 (-7d)	15 (±3d)	1 (±3d)	15 (±3d)	1 (±3d)	1 (±3d)	V801 (±7d)	V802-8XX (±14d)	
Procedure											
Survival Information									X		Survival information may be collected by contacting the patient or family directly (for example, via telephone) if no procedures are required. This should be collected approximately every 90 days.
Collection of post-study-treatment anticancer therapy information									X		Perform every 90 days for the first 2 years after discontinuation from study treatment and every 6 months (±14 days)] thereafter until death or study completion.
Patient-reported Outcomes											
• Worst pain NRS • Bowel movement diary • Bristol stool scale • Loperamide doses		X	X	X	X	X	X	X	X		Record daily for at least 3 days in the baseline screening period and continue daily following C1D1, and for the period between treatment discontinuation until the short-term follow-up visit (V801) is completed
• FACT GP5 • PRO CTCAE • EORTC IL36		X	X	X	X	X	X	X	X		Record at least once weekly during screening period, weekly during study treatment and at least once weekly following discontinuation until the short-term follow-up visit (V801) is completed
HCRU (Hosp, ER, analgesic, GF, transfusions)		X	X	X	X	X	X	X	X		Record weekly during screening, weekly during study treatment and at short-term follow-up
Genetic and biomarker collections											
Whole blood (for genetic analysis)			X								See Section 8.7. Collect sample for all participants, preferably at Cycle 1 Day 1 but can be

Study Period	Baseline		Study treatment (Cycle = 21 or 28 days)						Post-discontinuation		Instructions
Cycle/Visit	**Screening**		**Cycles 1**		**Cycle 2**		**Cycle 3**	**Cycle 4-n**	**Short-Term Follow-up[a]**	**Long-Term Follow-up[b]**	
Visit duration for Arm A (days)	Up to 28		28		28		28	28	30	90	
Visit duration for Arm B (days)	Up to 28		21 or 28		21 or 28		21 or 28	21 or 28	30	90	
Relative Day within Dosing Cycle & Visit Window	≤28	≤14	1 (-7d)	15 (±3d)	1 (±3d)	15 (±3d)	1 (±3d)	1 (±3d)	V801 (±7d)	V802-8XX (±14d)	
Procedure											
											collected at any time throughout the study.
Plasma (for biomarker collection)			Pre-dose Cycle 1						X		See Section 8.8. Collect pre-dose sample at C1D1 for all participants. Collect short term follow-up sample for participants only on Arm A who have PD after they have been on treatment for at least 12 months. Do not collect samples for participants on the chemotherapy arm at this visit.
Study Interventions											
Administer abemaciclib			X								See Section 6.1. C1D1 administration should occur within 7 days of randomization
Administer fulvestrant			X								See Section 6.1. C1D1 administration should occur within 7 days of randomization
Administer chemotherapy			X								See Section 6.1. C1D1 administration should occur within 7 days of randomization Chemotherapy includes capecitabine, docetaxel, nab-paclitaxel or paclitaxel.

Abbreviations: AE = adverse event; BP = blood pressure; C = Cycle; CT = computer tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); EORTC IL36 = European Organisation for Research and Treatment of Cancer quality of life questionnaire (abridged); ER = emergency room; FACT-GP5 = Functional Assessment of Cancer Therapy- Side Effects; GF = growth factor; HCRU = healthcare resources used; Hosp = hospitalization; ICF = informed consent form; MRI = magnetic resonance imaging; PD = progressive disease; PRO CTCAE = patient reported outcome Common Terminology Criteria for Adverse Events; Q12W = every 12 weeks; Q24W = every 24 weeks; QoL = quality of life; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer et al. 2009); V = Visit.

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

b Long-term follow-up begins when short-term follow-up period is completed and continues until death, study withdrawal, or the patient is lost to follow-up. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

Continued Access Schedule of Activities

Visit	Study Treatment	30-Day Follow-Up	Instructions
	501-5XX	901	
Procedure			
AE Collection	X	X	Per CTCAE v 5.0, for post follow-up, the investigator should only be made aware of collected SAEs related to study regimen or protocol procedures. Collect continuously at every visit and throughout the study.
Administer study intervention	X		See Section 6.1 for Study Intervention administration details and guidelines..

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event.

[a] Continued access follow-up begins when the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

[b] Efficacy assessments will be done at the investigator's discretion based on the standard of care.

2. Introduction

2.1. Study Rationale

Both the ASCO and NCCN guidelines recommend initial sequential use of ET-based treatment over cytotoxic chemotherapy in the treatment of HR+, HER2- MBC due to the superior benefit-risk profile of the former therapeutic strategy (Rugo et al. 2016; NCCN 2018). However, data from a survey of United States (US) oncologists suggests that cytotoxic chemotherapy may be initiated earlier in the course of MBC than recommended by consensus guidelines, potentially denying patients an effective and tolerable SOC ET-based therapy (Lin et al. 2016).

Study JPCU aims to compare the efficacy of ET fulvestrant in combination with abemaciclib, a CDK 4 and 6 inhibitor, to that of physician's choice of chemotherapy (capecitabine, docetaxel, nab-paclitaxel, or paclitaxel) in patients with HR+, HER2- MBC with at least 1 site of visceral metastases. Efficacy will be measured by the primary endpoint ORR.

2.2. Background

Breast cancer is the second most commonly diagnosed cancer and accounts for the second highest number of cancer deaths among women globally (CDC Breast Cancer). While the prognosis for locally occurring disease is typically promising, the outlook for MBC (metastatic breast cancer) is poor, with a median overall survival (OS) of 2 to 3 years and a 5-year survival rate of only ~25% (Harbeck and Gnant 2017; Cardoso et al. 2018).

Clinical decision-making for the management of patients with MBC takes into account multiple clinical factors such as HR/HER2 status, age, comorbidities, and patient preference. More specifically, treatment options for women with breast cancer are largely determined by tumor HR and HER2 status. For patients with HR+ HER2- MBC, treatment includes ET (e.g., anastrazole, letrozole, fulvestrant) alone or in combination with the CDK 4 and 6 inhibitors (such as abemaciclib, palbociclib, or ribociclib), as well as standard chemotherapy (e.g. capecitabine, docetaxel, paclitaxel, nab-paclitaxel [NCCN 2018; Waks and Winer 2019]). Growing evidence has suggested visceral metastasis and sites of metastases as potential prognostic factors for patients with HR+ MBC (Solomayer et al. 2000; Leone et al. 2017; Di Leo et al. 2018). Furthermore, possible improvements in treatment effect have been observed in patients with visceral metastases compared to non-visceral metastases (Di Leo et al. 2018).

"Visceral crisis" is a well described clinical syndrome characterized by rapid cancer progression causing fulminant or impending organ dysfunction (Cardoso et al. 2018). Regardless of HR and HER2 status, there is uniform agreement on the initiation of cytotoxic chemotherapy for patients in visceral crisis (Cardoso et al. 2016; Rugo et al. 2016; NCCN 2018). However, in the absence of visceral crisis, ASCO (Rugo et al. 2016) and NCCN 2019 guidelines recommend sequential use of ET-based treatment prior to the initiation of cytotoxic chemotherapy, due to the greater tolerability of the former class of agents (Cardoso et al. 2018). Nevertheless, a real-world retrospective Flatiron Health database analysis of HR+ HER2- metastatic breast cancer (MBC) patients, diagnosed and treated between 01 March 2017 to 28 February 2019 showed that of

2392 treated patients, 16.6% received chemotherapy as first line treatment while the most common first line treatments were CDK-based therapies (50% [Flatiron Health HER-derived database]). Of those receiving an ET as the first line therapy, 10.6% received chemotherapy as the second line of therapy. The most frequently used mono chemotherapeutics were paclitaxel, capecitabine, and nab-paclitaxel. The factors influencing choice of chemotherapy include new mechanism of action, response to prior therapies and tolerability of the chemotherapy. In a survey of community-based US cancer specialists, approximately 30% of physicians reported the presence of organ threatening disease or "visceral crisis" as the rationale for starting chemotherapy (Lin et al. 2016). These data suggest discontinuation of ET occurs earlier than recommended in favor of chemotherapy in spite of the less favorable tolerability profile of chemotherapy.

Abemaciclib, a potent inhibitor of the CDK 4 and 6 pathway, in combination with a non-steroidal aromatase inhibitor when administered as first-line treatment (Study I3Y-MC-JPBM) and the addition of abemaciclib in combination with fulvestrant as second-line treatment following disease progression on ET (Study I3Y-MC-JPBL) significantly improved progression-free survival (PFS) in patients with HR+ HER2- MBC (Goetz et al. 2017; Sledge et al. 2017). In addition, the combination treatment was generally well tolerated, with diarrhea and neutropenia being the only treatment emergent adverse events of Grade 3/4 severity occurring in more than 10% of patients (diarrhea [%]: 13/0; neutropenia [%]: 24/3 in Study I3Y-MC-JPBL [Sledge et al. 2017)). The overall positive benefit risk profile of abemaciclib in combination with fulvestrant is consistent with the overarching goal of current guidelines offering sequential ET until ET options have exhausted with HR+, HER2- MBC (Verzenio package insert). Importantly, the benefit from abemaciclib was observed in all patient subgroups including patients with poor prognostic features such as visceral metastases (Di Leo et al. 2018). Study I3Y-MC-JPCU will assess if abemaciclib and fulvestrant in combination have comparable efficacy, as defined in Section 9.1, to physician's choice of chemotherapy by measuring ORR in patients with HR+, HER2- MBC with the presence of visceral metastases.

2.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of abemaciclib are found in the Investigator's Brochure (IB), Patient Information Leaflet, Package Insert (PI), or Summary of Product Characteristics.

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of abemaciclib in combination with fulvestrant to chemotherapy	• ORR
Secondary	
• To further characterize the efficacy of abemaciclib in combination with fulvestrant compared to chemotherapy	• PFS • TTR • DoR • PFS2
• To compare the safety and tolerability of abemaciclib in combination with fulvestrant to chemotherapy	• Safety: including but not limited to TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE version 5.0
Exploratory/Tertiary	
• To evaluate PROs and HCRU for abemaciclib in combination with fulvestrant compared to chemotherapy	• PROs o Worst-pain NRS o BM Frequency o Bristol Stool Form Scale o Loperamide doses o FACT-GP5 o PRO-CTCAE o EORTC IL36 • HCRU o Hospitalization (reason, duration) o Emergency room visits (reason) o Analgesic use o Growth factor use o Transfusions use and type
• To assess the relationship between pharmacogenomics and clinical outcome	• Results of genetics and clinical outcome assessments
• To assess the relationship between biomarkers and clinical outcome	• Results of biomarkers and clinical outcome assessments

Abbreviations: BM = bowel movement; CTCAE = Common Terminology Criteria in Adverse Events; DoR = duration of response; TTR = time to response; EORTC IL36= European Organisation for Research and Treatment of Cancer quality of life questionnaire (abridged); FACT-GP5 = Functional Assessment of Cancer Therapy- Side Effects; HCRU = healthcare resources used; NRS = numeric pain rating scale; ORR = objective response rate; PFS = progression-free survival; PRO = patient reported outcome; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study JPCU is a multicenter, open-label, randomized-controlled study of abemaciclib, a CDK 4 and 6 inhibitor, in combination with fulvestrant compared to physician choice of standard chemotherapy in a patient population of post menopausal women with HR+, HER2- locally advanced or MBC who have poor prognosis due to visceral metastasis.

Patients will be randomized using the following stratification factors: the presence of liver metastases (Yes/No), sensitivity to prior ET (sensitive versus primary resistance versus secondary resistance), and postmenopausal status (natural/surgical/therapeutic radiation versus gonadotropin-releasing hormone [GnRH] agonist use).

Sensitivity to prior ET is defined as follows, and will be determined based on the patients' most recent sensitivity status. For example, if a patient met the definition of primary resistance on adjuvant ET and subsequently met the definition of secondary resistance on ET for MBC, the patient would be categorized as having secondary resistance.

1. Primary resistance: a relapse while on the first 2 years of adjuvant ET, or progressive disease (PD) within first 6 months of first-line ET for MBC, while on ET
2. Secondary resistance: a relapse while on adjuvant ET but after the first 2 years, or a relapse within 12 months of completing adjuvant ET, or PD ≥6 months after initiating ET for MBC, while on ET
3. Sensitive: patients who do not meet the definition of primary resistance or secondary resistance will be considered to be sensitive

Patients who meet all criteria for enrollment will be randomly assigned 1:1 to:

1. **Arm A**: abemaciclib in combination with fulvestrant, or
2. **Arm B**: physician choice of standard chemotherapy (capecitabine, docetaxel, nab-paclitaxel, or paclitaxel).

Cross over between study treatments is not allowed in this study. Additionally, post-discontinuation therapy is neither specified nor restricted.

Taken together, these data will be used to characterize the efficacy, safety and tolerability of abemaciclib in combination with fulvestrant compared to chemotherapy. Section 1.2 illustrates the study schema.

4.2. Scientific Rationale for Study Design

Study JPCU is a study in women participants with HR+ HER2- MBC with visceral metastasis, a poor prognostic feature which prompts some cancer specialists to initiate cytotoxic chemotherapy earlier than recommended by consensus treatment guidelines (Cardoso et al. 2016; Rugo et al. 2017; NCCN 2018). Visceral metastases and prior ET may typically steer a physician towards considering chemotherapy as a therapeutic choice. Eligible JPCU patients with visceral metastasis must have received at least 1 line of prior ET. Endocrine therapy may

have occured in either (or both) the (neo)adjuvant or metastatic setting; however, it must be limited to no more than 1 ET in the metastatic setting.

JPCU patients must be appropriate candidates for randomization to either abemaciclib-fulvestrant treatment or physician's choice of allowed chemotherapy agents (capecitabine, docetaxel, nab-paclitaxel or paclitaxel).

Patients will be randomized by a number of stratification factors thought to be associated with clinical outcomes to further reduce the potential for bias and improve the power of the analyses: namely sensitivity to prior ET, liver metastases, and postmenopausal status. Our internal data indicate that postmenopausal status is an important prognostic factor: in Study I3Y-MC-JPBL, the patients receiving GnRH agonist had a median PFS of 28.6 months versus 15.5 months for those patients who were naturally postmenopausal. As this study is assessing different methods of study intervention administrations, a Phase 4 open-label study is appropriate. The primary purpose of the study is to demonstrate that abemaciclib in combination with fulvestrant provides at least the same clinical benefit as chemotherapy to the patients, as defined by "comparability," and abemaciclib in combination with fulvestrant has a preferred safety profile over chemotherapy. An interim analysis of futility for ORR is planned.

4.3. Justification for Dose

Abemaciclib is Food and Drug Administration (FDA) and European Medicine Agency (EMA)-approved for use in combination with fulvestrant for the treatment of women with HR+, HER2-MBC with disease progression following ET. Justification for dose may be found in the IB and PI.

Justification for chemotherapy dosing is per package insert guidelines in association with physician's routine clinical practice for each agent.

4.4. End of Study Definition

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

Study completion will occur following the final analysis of primary and secondary objectives, as determined by Lilly.

5. Study Population

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

5.1. Inclusion Criteria

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

1. Must be able to provide informed consent, as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol, according to local regulations and are at least 18 years of age.
2. Must be patients who, in the opinion of the treating physician, are candidates suitable for randomization to single agent chemotherapy or abemaciclib/fulvestrant combination therapy
3. Must be female.
4. Must be of postmenopausal status due to natural cessation of ovarian function, surgery, therapeutic radiation or ovarian suppression with a GnRH agonist such as goserelin (initiated at least 28 days prior to Cycle 1 Day 1). Patients must meet at least 1 of the following criteria to document post-menopausal status:
    - prior bilateral oophorectomy
    - age ≥60 years, or
    - age <60 years, amenorrheic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and follicle-stimulating hormone (FSH) and estradiol levels in the postmenopausal range.
5. Must have a negative serum pregnancy test at baseline (within 14 days prior to randomization) and agree to use medically approved precautions to prevent pregnancy during the study and for 12 weeks following the last dose of abemaciclib if postmenopausal status is due to ovarian suppression with a GnRH agonist
6. Must have confirmed HR+, HER2- recurrent, locally advanced, unresectable, or MBC with evidence of relapse or disease progression on or following ET.
    - To fulfill the requirement for HR+ disease by local testing, a breast cancer must express, at least 1 of the hormone receptors (ER or progesterone receptor [PgR]). For ER and PgR assays to be considered positive, ≥1% of tumor cell nuclei must be immunoreactive by immunohistochemistry (IHC) (Hammond et al. 2010).
    - To fulfill the requirement of HER2- disease by local testing on most recent biopsy, HER2- negative tumor is determined as IHC score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH), as defined in the relevant ASCO/College of American Pathologists guidelines (Wolff et al. 2013).
7. Must have disease progression following at least 1 line of ET. ET may have been in the (neo)adjuvant or metastatic setting.

8. Must have metastatic disease with at least one site of visceral metastasis (e.g., pleura, lung, liver, peritoneum, omentum, ovary, or adrenal gland). Metastases to bone only is not permitted in this study.
9. Must have at least 1 measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al. 2009). If the patient has only 1 measurable lesion, and it has been previously radiated, then progressive disease must have occurred at least 28 days after completion of palliative radiotherapy.
10. Must be willing to participate for the duration of the study and to follow study procedures
11. Must be able to swallow tablets
12. Must have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 on the scale (Oken et al. 1982)
13. Must have discontinued all previous treatments for cancer and recovered from the acute effects of therapy. All patients who have experienced diarrhea as a side effect of prior therapies must have recovered to Grade 1 or less.

Patients must have discontinued from previous treatments, as shown below:

Previous Treatment	Length of Time Prior to Study Entry
Endocrine therapies	≥14 days
Cytotoxic therapies or targeted agents that are small molecule inhibitors	≥21 days or ≥5 half-lives, whichever is longer
Biologic agents that are large molecules including immunotherapy	≥28 days
Major surgery, excluding biopsy	≥28 days
Radiotherapy	
Limited-field radiotherapy with palliative intent	≥14 days
Other radiotherapy	≥28 days

14. Must have adequate organ function, as defined below:

System	Laboratory Value
Hematologic	
Absolute neutrophil count	$\geq 1.5 \times 10^9$/L
Platelets	$\geq 100 \times 10^9$/L
Hemoglobin	≥9 g/dL
Note: transfusions to increase a patient's hemoglobin level or initiation of erythropoietin or granulocyte-colony stimulating factor therapy to meet enrollment criteria are not allowed in the 14 days preceding the first dose of study drug. If a patient receives transfusions, erythropoietin, or granulocyte-colony stimulating factor therapy ≥14 days prior to the first dose, the hematologic criteria listed above must be met following the 14 day window and prior to the first dose of study therapy.	
Hepatic	
Total bilirubin	≤1.5×ULN Except patients with a documented history of Gilbert Syndrome who must have a total bilirubin level of <3.0×ULN
ALT and AST	≤3×ULN if there is no liver metastasis, **OR** ≤5×ULN if there are liver metastases
Renal	
Serum creatinine **OR**	≤1.5×ULN **OR**
Measured creatinine clearance **OR**	≥30 mL/min/1.73 m^2
Calculated creatinine clearance (Appendix 5)	

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

5.2. Exclusion Criteria

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

15. Have received prior systemic therapy (e.g., cytoxic chemotherapy, targeted treatment such bevacizumab, immunotherapy) for metastatic disease except ET
16. Have received more than 1 prior ET for metastatic disease.
17. Have visceral crisis including, lymphangitic spread, or leptomeningeal carcinomatosis, as determined by the treating physician. "Visceral crisis" is defined by the presence of visceral disease associated with impending or actual severe organ dysfunction due to rapid disease progression as assessed by clinically significant symptoms, signs and/or laboratory studies (Cardoso et al. 2018).
18. Have clinical evidence of symptomatic untreated central nervous system (CNS) metastases that may impede participation in this study. Patients with active untreated CNS metastasis are eligible if the investigator/treating physician has determined that CNS specific treatment (e.g., radiation) is not warranted and is not required and is unlikely to be required due to clinical and radiologic stability for the last 28 days preceding study screening. Screening for CNS metastases is not required for enrollment.
19. Have received prior treatment (for any duration) with fulvestrant or any CDK4/6 inhibitor.

20. Have received live vaccination within 28 days prior to randomization. Seasonal flu vaccinations that do not contain a live virus are permitted.
21. Have a personal history of any of the following conditions within the last 12 months:
    - syncope of cardiovascular etiology
    - ventricular tachycardia
    - ventricular fibrillation, or
    - sudden cardiac arrest
22. Have serious and/or uncontrolled preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study including interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea
23. Have any active and clinically relevant systemic bacterial, fungal or viral infection (for example, bacterial infection requiring intravenous [IV] antibiotics at time of initiating study treatment, fungal infection, human immunodeficiency virus or viral hepatitis, or detectable viral infection requiring systemic therapy). Screening is not required for enrollment.
24. Have inflammatory breast cancer or a history of any other cancer unless in complete remission with no therapy for a minimum of 3 years. Non-melanomatous skin cancer, carcinoma in-situ of the cervix and carcinoma in-situ of the bladder are the only exceptions to this exclusion criterion.
25. Have received an autologous or allogeneic stem-cell transplant.
26. Deleted.
27. Are breastfeeding.
28. Have initiated bisphosphonates or approved Receptor activator of nuclear factor kappa-B ligand targeted agents (for example, denosumab) <7 days prior to C1D1.
29. Are currently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
30. Have participated, within the last 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed from the last dose. Exceptions will be considered on a case by case basis by the Lilly clinical research physician (CRP)/clinical research scientist (CRS).

5.3. Lifestyle Considerations

Patients should refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products while on study due to the effect on cytochrome P450 (CYP)3A4 . Investigators are expected to review the appropriate product label for the standard chemotherapy treatment that he/she has proposed for the patient.

5.4. Screen Failures

Screen failures are defined as patients who consent to screening but do not meet 1 or more of the eligibility criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients 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. The interval between rescreening should be ≥2 weeks. Individuals may be rescreened a maximum of one time. The individual must sign a new ICF and will be assigned a new identification number. Repeating laboratory testing during the screening period or repeating screening tests to comply with the protocol designated screening period does not reconstitute rescreening. Repeat of laboratory testing is allowed once within the designated screening period.

6. Study Intervention

Study intervention is defined as any investigational intervention or marketed product intended to be administered to a study patient according to the study protocol.

6.1. Study Intervention(s) Administered

Arm	Arm A		Arm B
Intervention	Abemaciclib	Fulvestrant	Chemotherapy (capecitabine, docetaxel, nab-paclitaxel, or paclitaxel)
Dose	150 mg	500mg	Refer to PI/routine clinical practice
Schedule	BID	C1D1, C1D15, Day 1 of each subsequent cycle	Refer to PI/routine clinical practice
Route	PO	IM	Refer to PI

Abbreviations: BID = twice a day, at least 6 hours apart; C = Cycle; D = Day; IM = intramuscular; PI = package insert; PO = by mouth.

For the physician's choice of the four chemotherapies, it is expected that the investigator review appropriate product label/institutional guidelines for confirmation dosing (i.e., need for pre-medication, dose, schedule, toxicity management and dose modifications).

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 patients 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 record maintenance (i.e., 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.

Investigators should consult the study drug information provided in the Pharmacy Manual and on the Product Label for the specific administration information (including warnings, precautions, contraindications, adverse reactions, and dose modifications).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Patients will be randomized to 1 of 2 treatment arms, stratified by endocrine sensitivity status, presence of liver metastases and postmenopausal status. Stratification is intended to promote balance of known prognostic factors between treatment arms.

Randomization can occur up to 7 days prior to C1D1. Before a patient is randomized, the chemotherapy choice that the patient would receive if she was randomized to Arm B will be recorded in the Interactive Web Response System.

6.4. Study Intervention Compliance

Patient compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets/capsules, etc. Deviation from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

Some study intervention will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured.

A patient will be considered noncompliant if he or she takes <75% of the planned doses for assigned study drug in a cycle. A patient will also be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken ≥125% of the planned doses of study drug in a cycle.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient 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 patient'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 (AUC) to abemaciclib by 3.4-fold (Study I3Y-MC-JPBE) and coadministration of rifampin, a strong CYP3A inducer, decreased exposure to abemaciclib by 95% (Study I3Y-MC-JPBF). Therefore, grapefruit or grapefruit juice as well as inducers and inhibitors of CYP3A should be substituted or avoided if possible (Appendix 7).

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

If coadministration with a strong CYP3A inhibitor is unavoidable, investigators should consult the study drug information provided on the Product Label for dose adjustment recommendations. Specifically for coadministration with the strong CYP3A inhibitor ketoconazole, the abemaciclib dose should be reduced to 50 mg twice daily.

Abemaciclib and its major active metabolites inhibit the renal transporters organic cation transporter 2, multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K. In vivo interactions of abemaciclib with clinically relevant substrates of these transporters, such as creatinine, may occur.

Based on the in vitro inhibition of P-glycoprotein and breast cancer resistance protein observed with abemaciclib, in vivo interactions of abemaciclib with narrow therapeutic index substrates of these transporters, such as digoxin, may occur.

In clinical studies in patients with breast cancer, no clinically relevant pharmacokinetic drug interactions were observed between abemaciclib and anastrozole, exemestane, fulvestrant, letrozole, or tamoxifen.

The Lilly CRP should be contacted if there are any questions regarding concomitant or prior therapy. No other chemotherapy, immunotherapy, herbal supplements and/or herbal drugs intended to treat cancer, or experimental drugs will be permitted while the patients are on this study.

6.5.1. Palliative Medicine and Supportive Care

Palliative radiation therapy is permitted for irradiating small areas of painful metastases that cannot be managed adequately using systemic or local analgesics after discussion with and agreement of the Lilly CRP or designee. Such areas must not be an identified target lesion and must not constitute progressive disease or meet RECIST criteria for progressive disease. 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 therapy.

In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the case report form (CRF). Replacement hormonal therapy (e.g., thyroid or adrenocorticoid supplementation) will be allowed. Post-menopausal hormone replacement therapy (e.g., estrogen or progesterone agents) is not allowed.

Patients 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.

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).

Megestrol acetate use is not permitted for this study.

All concomitant medications should be recorded throughout the patient's participation in the study.

6.5.2. Supportive Management for Diarrhea in Patients Receiving Abemaciclib

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

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (e.g., loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours to at least Grade 1 (per CTCAE v 5.0), study abemaciclib treatment should be suspended until diarrhea is resolved to at least Grade 1.
- When abemaciclib treatment recommences, dosing should be adjusted as outlined in Section 6.6.1. In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

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

Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid and electrolyte replacement as clinically indicated.

6.5.3. Bisphosphonates and Receptor Activator of Nuclear Factor Kappa-B Ligand (RANK-L) Targeted Agents

Patients with bone metastases present on baseline imaging should be appropriately treated with bisphosphonates or RANK-L targeted agents (for example, denosumab), per respective approved labels. Initiation of treatment with bone-modifying agents must begin at least 7 days prior to randomization. Patients receiving bisphosphonates or RANK-L targeted agents should not switch treatments (for example, replace a bisphosphonate with denosumab) while on study treatment. However, exceptional cases without evidence of PD may be considered in consultation with the CRP. These exceptional cases will not incur a protocol deviation.

6.6. Dose Modification

6.6.1. Abemaciclib

Please refer to the following tables for dose modifications for adverse reactions related to abemaciclib. If dose reduction is necessary, decrease the dose by 50 mg at a time. Discontinue abemaciclib for patients unable to tolerate 50 mg twice a day, at least 6 hours apart(BID).

Abemaciclib dose modification for adverse reactions

Dose Level	Abemaciclib dose in combination with fulvestrant
Recommended 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 a day, at least 6 hours apart.

Abemaciclib dose modification and management- hematologic toxicities[a]

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.

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

[a] If blood cell growth factors are required, 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 at next lower dose unless already performed for the toxicity that led to the use of the growth factor. Growth factor use as per current treatment guidelines.

Abemaciclib dose modification and management- diarrhea

At the first sign of loose stools, start treatment with antidiarrheal agents and increase intake of oral fluids.	
CTCAE Grade	**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	Suspend dose until toxicity resolves to ≤Grade 1. Resume at next lower dose.

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

Abemaciclib dose modification and management - increased ALT/AST

CTCAE Grade for ALT and AST	**Abemaciclib dose modifications**
Grade 1 (>ULN-3.0 x ULN) Grade 2 (>3.0-5.0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	No dose modification is required.
Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Elevation in AST and/or ALT >3 x ULN WITH total bilirubin >2 x ULN, in the absence of cholestasis	Discontinue abemaciclib.
Grade 4 (>20.0 x ULN)	Discontinue abemaciclib.

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

Abemaciclib dose modification and management - interstitial lung disease/pneumonitis

CTCAE Grade	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.

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

Abemaciclib dose modification and management - nonhematologic toxicities excluding diarrhea, increased ALT/AST, and ILD/pneumonitis

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. Resume at next lower dose.
Grade 3 or 4	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

6.6.2. Dose Suspension and Cycle Delay

Both dose suspension (within a cycle) and cycle delay are permitted. Study treatment may be held up to 14 days within a cycle or at start of next cycle to permit sufficient time for recovery from the toxicity. Patients not recovering from toxicity within 14 days should be considered for discontinuation. In exceptional circumstances, a delay >14 days is permitted upon agreement between the investigator and the Lilly CRP.

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 CRP.

6.6.3 Fulvestrant and Chemotherapeutic Agents

Refer to local PI and label for dose adjustments related to fulvestrant or any of the chemotherapeutic agents in the study. There is no cross-over between treatment arms in this study. In addition, patients in the abemaciclib plus fulvestrant arm who develop unacceptable toxicity owing to abemaciclib must discontinue abemaciclib and may remain on fulvestrant; patients who develop unacceptable toxicity due to fulvestrant must discontinue fulvestrant and may remain on abemaciclib.

6.7. Intervention after the End of the Study

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

6.7.1. Treatment after Study Completion

Study completion will occur following the final analysis of primary and secondary objectives, as determined by Lilly. Investigators will continue to follow the SoA (Section 1.3) for all patients until notified by Lilly that study completion has occurred.

6.7.1.1. Continued Access

Patients who are still on study intervention (i.e., study treatment) at the time of study completion may continue to receive study intervention if they are experiencing clinical benefit and no undue risks. The continued access period will apply to this study only if at least 1 patient is still receiving study intervention when study completion occurs. Lilly will notify investigators when the continued access period begins. Lilly may allow patients to enroll in a "rollover" protocol to provide long-term continued access for patients enrolled in this study.

Patients are not required to sign a new ICF before treatment is provided during the continued access period; the initial ICF for this study includes continued access under this protocol.

The continued-access period will begin after study completion and ends at End of Study. The patient's continued access to study intervention will end when a criterion for discontinuation is met (Section 7). Continued-access follow-up will begin when the patient and the investigator agree to discontinue study intervention and lasts approximately 30 days. Follow-up procedures will be performed as shown in the SoA (Section 1.3).

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

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

7. Discontinuation of Study Intervention and Patient Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

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

- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- patient decision
    - the patient or the patient's designee (for example, parents or legal guardian) requests to discontinue study product
- sponsor decision
- investigator decision

In addition, patients will be discontinued from study treatment in the following circumstances:

- The patient becomes pregnant during the study
- The patient is significantly noncompliant with study procedures and/or treatment
- Disease progression (as defined by RECIST v1.1).
- Unacceptable toxicity
- The patient, for any reason, requires treatment from another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from abemaciclib will occur prior to introduction of the new agent
- If the investigator decides that the patient should be discontinued from study treatment

Patients discontinuing from the investigational product prematurely for any reason should complete AE and other follow-up procedures per Section 1.3 (SoA), Section 8.3 (AEs and SAEs), and Section 8.2 (Safety Assessments) of the protocol.

7.2. Patient Discontinuation/Withdrawal from the Study

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- subject decision
    - the patient or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study

- The patient becomes pregnant during the study. See Section 8.3 regarding regulatory reporting requirements on fetal outcome.

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 1.3 (SoA), Section 8.3 (AE and SAE), and Section 8.2 (Safety Assessments) of this protocol.

7.2.1. Discontinuation of Inadvertently Enrolled Patients

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

If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product.

Safety follow up is as outlined in Section 1.3 (SoA), Section 8.3 (AEs and SAEs), and Section 8.2 (Safety Assessments) of the protocol.

7.3. Lost to Follow-Up

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

Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the patient will not be considered lost to follow-up.

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

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.7.2.

8. Study Assessments and Procedures

- Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.
- Study procedures and their timing are summarized in the SoA (Section 1.3). 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 patient should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Tumor assessments will be performed for each patient as shown in the SoA (Section 1.3). RECIST v1.1 (Eisenhauer et al. 2009) will be applied as the primary criteria for assessment of tumor response and date of tumor progression. Tumor assessment will be performed until documented PD as per the RECIST v1.1 criteria, initiation of new anticancer therapy, discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), or completion of the study, whichever occurs first.

The following general guidelines will apply:

- A positron emission tomography (PET) scan alone or as part of a PET-computer tomography (CT) scan may be performed separately as part of routine clinical care but cannot be used for tumor assessment.
- It's recommended that the CT scans of the abdomen and pelvis be performed with IV contrast, whenever possible. For patients with known hypersensitivity to CT contrast material, a CT scan of the chest without contrast and gadolinium-enhanced MRI of the abdomen and pelvis are encouraged.

- The CT portion of a PET-CT scan may be used as a method of response assessment if the site can document that the CT is of similar diagnostic quality to a diagnostic CT (i.e., with intravenous and oral contrast).
- The same measuring modality must be used consistently throughout study for tumor assessment.
- Measurements should be performed on schedule even in the event of study treatment delay or omission.
- Imaging delays due to patient deterioration will not be considered a protocol deviation.
- Patients who discontinue study treatment without document progressive disease should continue to undergo clinical/radiologic tumor assessment until progressive disease is documented per RECIST 1.1 criteria, death, or study completion, whichever occurs first.

Bone scintigraphy and tumor assessment in patients with bone metastases

- Please refer to the SoA (Section 1.3) for assessment timelines.
- Bone scintigraphy will be performed in all patients. Prior bone scintigraphy, obtained within 45 days of C1D1 as part of routine clinical care, may serve as the baseline bone scintigraphy.
- Bone scintigraphy should be repeated to confirm complete response (CR) or performed as clinically indicated (e.g. new or worsening bone pain, or increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases).
- Bone scintigraphy should be repeated every 24 weeks after a CR is confirmed.
- For patients with new lesions identified by post-baseline bone scintigraphy , targeted assessments by X-ray, CT scan with bone windows, or MRI will be performed to confirm findings.

  Bone lesions identified at baseline will follow the same assessment schedule as for measurable lesions.

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) will be provided to investigative 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.

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, if a central vendor is used for the clinical trial.
- See Appendix 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 patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or until the completion of V801 should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - 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, must be conducted in accordance with the laboratory manual and the SoA.
    - If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (for example, blood pressure increased, neutrophils decreased, etc.) and it is known to be related to a disease diagnosis (for example, hypertension, neutropenia, etc.), this should be entered into the CRF. Do not enter the test abnormality, enter the disease diagnosis or categorical term.
    - If laboratory values from non-protocol specified laboratory assessments require a change in patient management (e.g., dose modification) or are considered clinically significant by the investigator (e.g., AE or SAE), then the event(s) results must be recorded in the CRF.

8.2.1.1. Hepatic Safety Monitoring

Liver testing (Section 10.4), including alanine aminotransferase (ALT), aspartate aminotransferase (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 1 or more of these conditions occur:

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

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), and 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 (international normalization ratio); serological tests for viral hepatitis A, B, C, E, and autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or 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 liver biopsy.

Additional Hepatic Safety Data Collection

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

In participants enrolled with baseline ALT or AST <1.5x ULN

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

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

- Elevated ALT or AST ≥3x baseline on 2 or more consecutive tests
- The combination of elevated ALT or AST ≥2x baseline and elevated TBL ≥2x 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 an SAE

8.2.1.2. Venous Thromboembolic Events (VTEs)

In the randomized Phase 3 studies in breast cancer participants (Studies JPBL and JPBM, abemaciclib in combination with ET), there was a greater number of participants who experienced VTEs in the abemaciclib plus endocrine therapy arm than in the placebo plus endocrine therapy arm. The majority of the events were non-serious and were treated with low-molecular-weight heparin. Generally, these events did not result in discontinuation of the study treatment. In Study JPCG, a greater number of participants experienced VTE events in the

abemaciclib plus tamoxifen arm compared with the abemaciclib monotherapy arms. No events of VTE resulted in death or discontinuation of the study treatment and most patients were treated with low-molecular-weight heparin. In studies with single-agent abemaciclib use in the MBC population or other tumor types, including non-small cell lung cancer, no increased rates of VTEs were observed as compared to the incidence of VTEs for these particular patient populations who were treated with other anticancer agents. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. VTEs have been reported with other CDK4 and 6 inhibitors and endocrine therapy is known to be associated with the occurrence of VTEs. Participants should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate.

8.2.1.3. 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 ioxhexol 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 (BUN), 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 non-hematological toxicities.

8.2.1.4. Interstitial Lung Disease (ILD)/Pneumonitis

Interstitial lung disease/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 CT, broncheoalveolar lavage, and biopsy as clinically indicated.

Refer to Section 6.6.1 for guidance on dose adjustments of abemaciclib for patients with ILD/pneumonitis (see Appendix 6 for ILD/pneumonitis Common Terminology Criteria for Adverse Events [CTCAE] grades). Discontinue abemaciclib in cases of severe ILD/pneumonitis.

8.3. Adverse Events and Serious Adverse Events

The investigator should provide AE verbatim terms and then the terms will be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory

Activities (MedDRA) Lower Level term (LLT) dictionary. The investigator will use CTCAE v 5.0 to assign AE severity grades.

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is otherwise explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

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

After the ICF is signed, study site personnel will record via CRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

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

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization

- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the CRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 8.3.1) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic AE should have additional data collected using the CRF..

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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.

Suspected Unexpected Serious Adverse Reactions

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

that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

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

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE section of the CRF.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of investigator awareness. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. SAEs, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

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

8.3.2. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 1.3).

8.3.3. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of 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.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., 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.

8.3.4. Pregnancy

This section is not applicable as the patient population being evaluated is post-menopausal women (refer to Section 5 for additional details).

8.3.5. Cardiovascular and Death Events

Not applicable.

8.3.6. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study patients, monitor quality, and to facilitate process and product improvements.Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

8.4. Treatment of Overdose

Refer to the IB and/or Product Label for intervention or comparator for available information on the signs, symptoms, and treatment of overdose.

8.5. Pharmacokinetics

Not applicable

8.6. Pharmacodynamics

Not applicable

8.7. Genetics

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to study treatment and to investigate genetic variants thought to play a role in breast cancer. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of study treatment.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome and exome

sequencing, genomewide association studies and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

8.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid, ribonucleic acid, proteins, lipids, and other cellular elements.

This study will analyze biomarkers relevant to abemaciclib, mechanism of action of study treatment, the variable response to study drug(s), immune function, tumor microenvironment, and pathways associated with cancer. These samples may also be used to develop related research methods or to validate diagnostic tools or assays.

Plasma sample for biomarker research will be collected at the times specified in the Schedule of Activities (Section 1.3) where local regulations allow. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon by the investigator and Lilly.

It is possible that biomarker data for patients in the study has already been generated from samples that were collected and analyzed prior to enrolling in this study. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Section 8.8.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum 15 years after the last participant visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of study treatment.

Technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, gene expression assays and protein measurements may be performed on these samples to assess potential associations between these biomarkers and clinical outcomes.

8.9. Medical Resource Utilization and Health Economics

The self-reported questionnaires will be administered according to the SoA (Section 1.3) in countries where the questionnaires have been translated into the native language of the region and linguistically validated. Patient-reported questionnaires should be completed by patients when a language translation is available in which the patient is fluent or literate.

8.9.1. Patient-Reported Outcomes (PRO)

The following PROs will be measured using an electronic device:

- Worst-pain numeric pain rating scale (NRS)
- Bowel movement (BM) frequency
- Bristol Stool Form Scale
- Loperamide doses
- Functional Assessment of Cancer Therapy- Side Effects (FACT-GP5)
- Patient reported outcome-Common Terminology Criteria in Adverse Events (PRO-CTCAE)
- European Organisation for Research and Treatment of Cancer quality of life questionnaire (abridged) (EORTC IL36)

Worst-pain NRS is a single item that asks about worst pain in the past 24 hours.

Use of pain medication will be assessed in conjunction with the worst-pain assessment. Data on each individual prescription and over-the-counter analgesic medication will be recorded on the Concomitant Medications eCRF. The use of pain medications should be reviewed with the patient at each subsequent visit. Any changes to analgesic use (new or stopped analgesics) will be recorded on the eCRF. Pain medication will be classified into medication categories, using the World Health Organization analgesic ladder. A medication category will be assigned based on the maximum analgesic therapy administered for that cycle on a routine basis.

BM frequency is a single item that asks about bowel movement frequency.

Bristol Stool Form Scale is a single item that asks about stool form (Lewis et al. 1997).

Loperamide doses is a single item that asks about number of loperamide doses.

The **FACT GP5** is a single item from the FACT-G questionnaire that asks about how bothered the patient is about the side effects of treatment (Cella et al. 1993).

PRO-CTCAE is a patient-reported outcome measurement system developed by the National Cancer Institute to collect symptomatic AEs from cancer patients enrolled in clinical trials (Bash et al. 2014; Dueck et al. 2015). The PRO CTCAE item library includes 78 symptomatic AE and a total of 124 total items- some AEs include multiple items (e.g. frequency and/or severity and/or interference [NCI 2018]). From this item library, 15 AEs (29 total items) were selected based on the most frequent patient-felt AEs reported in MONARCH 2 and the chemotherapy comparator FDA labels.

The **EORTC IL36** is an abridged 17-item version of the 30-item EORTC QLQ-C30 (Aaronson et al. 1993). This version omits the 13 Symptom items and consists solely of the Global Health and Functional scales:

- global health status/quality of life (2 items)
- functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning)

The full EORTC QLQ-C30 is broadly used in cancer trials, validated, and available in over 80 different languages.

For each PRO, the population will include all patients who completed at least 1 baseline followed by at least 1 postbaseline assessment.

8.9.2. Healthcare Resource Utilization

Data, associated with medical encounters, will be collected per SoA (Section 1.3) in the CRF by the investigator and study-site personnel for all patients.

Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to describe utilization between arms and will include:

- Hospitalizations (reason and duration)
- Emergency room visits (reason)
- Analgesic use (and other relevant concomitant medication as needed)
- Growth factor use
- Transfusions: use and type

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary objective of the study is to assess the comparability of abemaciclib in combination with fulvestrant (Arm A) to chemotherapy (Arm B) with respect to ORR. Progression-free survival comparability is an important secondary endpoint for the study, and will be assessed only if ORR comparability is declared, using a gatekeeping testing strategy. The comparability will be declared if there is high confidence (i.e., 80% posterior probability) that the true effect of Arm A is not worse than that of Arm B by more than a specified margin.

The hypotheses to be tested are:

- ORR comparability: There is at least an 80% posterior probability that true $ORR_{Arm\ B}$ – true $ORR_{Arm\ A} < 10\%$, where 10% is the defined margin for ORR comparability
- PFS comparability (gated secondary endpoint): There is at least an 80% posterior probability that true PFS hazard $ratio_{Arm\ A/Arm\ B} - 1 < 0.2$, where 0.2 is the defined margin for PFS comparability.

9.2. Sample Size Determination

Approximately 300 patients will be randomized in a 1:1 ratio to Arm A and Arm B for an estimated total of 150 patients per arm.

The primary analysis of ORR to assess ORR comparability will be performed approximately 6 months after last patient entering treatment; the final analysis of PFS to assess PFS comparability will be performed, if ORR comparability is declared, when approximately 180 PFS events in total have been observed.

ORR

Comparability of ORR will be declared if the following Bayesian criterion is achieved in the primary ORR analysis:

$$\text{Posterior P}(\text{true ORR}_{Arm\ B} - \text{true ORR}_{Arm\ A} < 10\%) > 80\%$$

Full detail regarding the Bayesian model for ORR (including prior specifications) will be provided in the statistical analysis plan (SAP).

CCI [redacted]

- CCI [redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

PFS

Progression-free survival comparability will be declared if ORR comparability is declared AND the following Bayesian criterion is achieved in the final PFS analysis:

$$\text{Posterior P}\,(HR - 1 < 0.2) > 80\%, \text{ where HR} = \text{true hazard}_{\text{Arm A}} / \text{true hazard}_{\text{Arm B}}$$

Full detail regarding the Bayesian model for PFS (including prior specifications) will be provided in the SAP.

Simulations were conducted to evaluate number of PFS events and probability of declaring
CCI [redacted]

[redacted]

- [redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

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

CCI [redacted]

9.3. Populations for Analyses

The following analysis sets will be defined for this study:

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

Safety population: will include all randomized patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the first dose of study treatment a patient actually received, regardless of the arm to which he or she was randomized. The safety analysis set will be used for all dosing/exposure, safety analyses, and health economics analyses.

9.4. Statistical Analyses

9.4.1. General Statistical Considerations

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

Posterior medians and Bayesian credible intervals will be reported for the endpoints (ORR and PFS) for which Bayesian analyses have been specified.

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

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.4.2. Efficacy Analyses

Objective Response Rate is defined as the number of patients who achieve a best overall response of CR or partial response (PR) divided by the total number of patients randomized to the corresponding treatment arm (ITT population), based on investigator-assessed tumor responses. Confirmations of CR and PR are not required. Primary comparison between treatment arms will be based on the Bayesian decision rule as described in Section 9.2. The 80th percentile of the posterior distribution for the difference in true ORR (true $ORR_{Arm\ B}$ – true $ORR_{Arm\ A}$) will be calculated and compared to 10%. In addition, the median of the posterior distribution for ORR, with 95% equal-tailed credible interval, will be summarized for each treatment arm.

Progression-free Survival is defined as the time from randomization until the first occurrence of documented disease progression per RECIST 1.1 criteria, or death from any cause in the absence of progressive disease. Progression-free survival will be based on investigator-assessed tumor responses; there will not be an independent central review of imaging data. Patients known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment (a detailed PFS event/censoring scheme is provided in the table below). A (stratified) Bayesian Cox regression model will be used to estimate the PFS HR comparing Arm A and Arm B. The 80th percentile of the posterior distribution of the HR comparing Arm A and Arm B will be calculated and compared to 1.2. In addition, the posterior medians and associated 95% credible intervals for true median PFS by treatment arm will be provided. Sensitivity analyses for PFS will be described in the SAP.

Progression-free Survival 2: Since exact progression date on post-therapies may not be available, in general, progression-free survival 2 (PFS2) is defined as the time from randomization to the discontinuation date of next-line (first line of post-discontinuation treatment), or starting date of the second line of post-discontinuation treatment or death from any cause, whichever is earlier. If the patient is alive at the cutoff for analysis, and a PFS2 event has not been observed, PFS2 data will be censored on the last date the patient was known to be alive. A detailed definition of PFS2 will be described in the SAP.

PFS Event/Censoring Scheme

Situation	Date of Event or Censor	Event / Censor
Tumor progression or death	Earliest date of PD or death	Event
No tumor progression and no death	Date of last adequate radiological assessment or date of randomization (whichever is later)	Censored
Unless		
No baseline radiological tumor assessment available	Date of randomization	Censored
No adequate post baseline radiological tumor assessment available and death reported after 2 scan intervals following randomization	Date of randomization	Censored
New anticancer treatment started (excluding maintenance endocrine therapy following chemotherapy) and no tumor progression or death within 14 days	Date of adequate radiological assessment prior to (start of new therapy +14 days) or date of randomization (whichever is later)	Censored
Tumor progression or death documented immediately after 2 or more scan intervals following last adequate radiological tumor assessment or randomization (whichever is later)	Date of last adequate radiological assessment or date of randomization (whichever is later)	Censored

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; SAP = statistical analysis plan; SD = stable disease.

Notes:

(1) Symptomatic deteriorations (i.e. symptomatic progressions, which are not radiologically confirmed) will not be considered as progression

(2) Adequate radiological tumor assessment refers to an assessment with one of the following responses: CR, PR, SD or PD

(3) For definition of 2 scan intervals, including any adjustment for scan window, see SAP

Time to Response

Time to Response (TTR) is defined as the time from randomization until the date that measurement criteria for CR or PR (whichever is first recorded) are first met, per RECIST v1.1.

Duration of Response

Duration of response is defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or documented disease progression is observed, per RECIST 1.1 criteria, or the date of death from any cause in the absence of documented disease progression or recurrence.

9.4.3. Safety Analyses

All patients in the safety analysis set will be evaluated for safety and toxicity.

The MedDRA Version (25.0x [or higher]) will be used when reporting AEs by MedDRA terms. The MedDRA LLT 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 (PT) within the System Organ Class.

Safety analyses will include summaries of the following:

- AEs, including severity in CTCAE grade and possible relationship to study drug
- SAEs, including possible relationship to study drug
- AEs leading to dose adjustments
- discontinuations from study treatment due to AEs or death
- treatment emergent abnormal changes in laboratory values
- treatment emergent abnormal changes in vital signs

9.4.4. Other Analyses

9.4.4.1. Patient-Reported Outcome (PRO)

The number of missing and incomplete questionnaires/assessments will be summarized for each instrument by visit and treatment arm, overall by treatment arm, and overall for the trial (all visits, all treatment arms).

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

- Worst-pain NRS
- BM Frequency
- Bristol Stool Form Scale
- Loperamide doses
- FACT-GP5
- PRO CTCAE
- EORTC IL36

For each patient with data from baseline and at least 1 other visit, the maximum change from baseline score will be calculated and summarized for PRO CTCAE, EORTC functional and quality of life (QoL) scores.

EORTC IL36 instrument data will be scored as described by Aaronson et al. 1993. If not already addressed in the EORTC scoring manual (Fayers et al. 2001), descriptive statistics for each EORTC IL36 will be calculated and evaluated between arms.

Further patient-reported analysis details will be described in the SAP.

9.4.4.2. Medical Resource Utilization

Utilization data will be summarized descriptively by healthcare resources used (HCRU) category (hospitalization days and reasons, emergency room visit reasons, growth factor use, analgesic use and transfusions), including a frequency table with tabular statistics. For categorical variables, frequency and the corresponding percentage will be derived and measures of central tendency and variability will be calculated for continuous variables by arm. Tests for differences

in proportion between treatment groups and between response groups may be performed as warranted (Chi-square for categorical variables, t-test for continuous variables and non-parametric tests for non-normally distributed data).

Further utilization analysis details will be described in the SAP.

9.4.4.3. Subgroup Analyses

A prespecified list of subgroups will be identified in the SAP. The treatment effect within each subgroup will be summarized. Subgroup analyses will include choice of chemotherapy prior to randomization. Other subgroup analyses not specified in the SAP may be performed as deemed appropriate. These subgroups will be based on important characteristics, for example, prognostic significance.

9.4.4.4. Patient Disposition

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

9.4.4.5. Patient Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target patient population considered for regulatory approval.

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

9.4.4.6. Concomitant Therapy

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

9.4.4.7. Treatment Compliance

Study treatment that is administered intravenously 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.

9.4.4.8. Biomarker Analyses

Biomarker analyses will be based on the subset of all enrolled patients from whom a valid assay result (according to laboratory guideline) has been obtained. Correlative analyses will be performed to investigate associations between biomarkers and clinical endpoints as deemed appropriate.

An exploratory objective of this study is to evaluate biomarkers relevant to abemaciclib, mechanism of action, the variable response to study drug(s), immune function, tumor microenvironment, and pathways associated with cancer.

9.5. Interim Analyses

One interim analysis of futility for ORR will be conducted approximately 6 months after the 100th patient has been randomized. The futility rule is described as follows:

$$\text{Posterior P}(\text{true ORR}_{\text{Arm B}} - \text{true ORR}_{\text{Arm A}} < 10\%) < 20\%$$

An assessment committee (AC) will be established to conduct interim analysis. The AC will include, at a minimum, Lilly Oncology Medical Director and statistician; Lilly study CRP/CRS will be excluded from the AC. Details on AC membership will be described in the Lilly Interim Analysis Authorization Form. Although the decision at the interim analysis will be made primarily based on the futility rule, AC members will also review and consider the totality of interim data to determine whether there are sufficient evidence to justify the termination of study treatment and/or enrollment due to futility.

10. Supporting Documentation and Operational Considerations

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 International Council for Harmonisation (ICH) GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., 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 patients.
- 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 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

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

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

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 patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients 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 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 patient 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.
- Patients 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 patient or the patient's legally authorized representative and is kept on file.

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

10.1.3. Data Protection

- Patients will be assigned a unique identifier by the investigator. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient 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 patient.
- The patient 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.

10.1.4. Dissemination of Clinical Study Data

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

10.1.5. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and verify data reported to detect potential errors

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

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

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.

Additionally, electronic Clinical Outcome Assessment (eCOA) data (questionnaires, scales, self-reported diary data, rating scales etc.) will be directly recorded by the subject, into an instrument (for example, hand held smart phone or tablet, or by means of an interactive voice/web system). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data.

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 the results will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

10.1.6. Source Documents

- Source documents provide evidence for the existence of the patient 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 Closure

10.1.7.1. Discontinuation of the Study

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

10.1.7.2. Discontinuation of Study Sites

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

10.2. Appendix 2: Clinical Laboratory Tests

- Local laboratory results are only required in the event that the central laboratory results are not available in time for inclusion/exclusion determination, study intervention administration, and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (e.g., blood pressure increased, neutrophils decreased, etc.) and it is known to be related to a diagnosis (e.g., hypertension, neutropenia, etc.) this should be entered into the CRF. Do not enter the test abnormality, enter the diagnosis or categorical term.
- Protocol-specific requirements for inclusion or exclusion of patients 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.

Investigators must document their review of each laboratory safety report. Enrollment and treatment decisions may be based upon local laboratory results. Discrepancies between local and central laboratory results will not be considered a protocol deviation.

Clinical Laboratory Tests

Hematology[a] **-**Local laboratory	
Leukocytes (WBC)	Basophils
Neutrophils	Erythrocytes (RBC)
Lymphocytes	Hemoglobin (HGB)
Monocytes	Hematocrit (HCT)
Eosinophils	Platelets (PLT)
Coagulation -Local laboratory	
PT/INR	PTT
Urinalysis -Local laboratory	
Blood	Protein
Glucose	Specific gravity
Ketones	Urine leukocyte esterase[b]
pH	
Clinical chemistry[a] **-** Central laboratory	
Serum concentrations of:	
ALT	Chloride
Albumin	Creatinine
Alkaline phosphatase	Glucose (random)
AST	Potassium
TBL	Protein
BUN or blood urea	Sodium
Calcium	
Pregnancy Test (only for participants receiving ovarian suppression with a GnRH agonist) - Local laboratory	
Serum pregnancy test	
Postmenopausal Confirmation Testing (only for participants <60 years, and amenorrheic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression)**) -** Local laboratory	
FSH	Estradiol
Cystatin C- if clinically indicated	
Cystatin C	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRF = case report form; FSH = follicle stimulating hormone; GnRH = gonadotropin-releasing hormone; RBC= red blood cells; TBL = total bilirubin; WBC = white blood cells.

a Treatment and enrollment decisions may be based on local laboratory results.

b Urine microscopy may be used in place of the urine leukocyte esterase assessment to test for the presence of WBCs.

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.

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

No additional pregnancy information (other than that included in Section 1.3) will be collected in this study).

Please follow the contraceptive guidelines below.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Intrauterine device (IUD)
• 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 90 days.)*
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 amenorrhoea method (LAM) 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).

10.4. Appendix 4: 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 patients in consultation with the Lilly, or its designee, CRP.

<table>
<tr><td colspan="2">Hepatic Evaluation Testing – Refer to protocol Hepatic Safety Monitoring Section 8.2.1.1 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 <u>in addition to central testing</u> when required for immediate patient management.
• Results will be reported if a validated test or calculation is available.</td></tr>
<tr><td>Hematology</td><td>Clinical Chemistry</td></tr>
<tr><td>Hemoglobin</td><td>Total bilirubin</td></tr>
<tr><td>Hematocrit</td><td>Direct bilirubin</td></tr>
<tr><td>Erythrocytes (RBCs - Red Blood Cells)</td><td>Alkaline phosphatase (ALP)</td></tr>
<tr><td>Leukocytes (WBCs - White Blood Cells)</td><td>Alanine aminotransferase (ALT)</td></tr>
<tr><td>Differential:</td><td>Aspartate aminotransferase (AST)</td></tr>
<tr><td>Neutrophils, segmented</td><td>Gamma-glutamyl transferase (GGT)</td></tr>
<tr><td>Lymphocytes</td><td>Creatine kinase (CK)</td></tr>
<tr><td>Monocytes</td><td>Other Chemistry</td></tr>
<tr><td>Basophils</td><td>Acetaminophen</td></tr>
<tr><td>Eosinophils</td><td>Acetaminophen Protein Adducts</td></tr>
<tr><td>Platelets</td><td>Alkaline Phosphatase Isoenzymes</td></tr>
<tr><td>Cell morphology (RBC and WBC)</td><td>Ceruloplasmin</td></tr>
<tr><td rowspan="2">Coagulation</td><td>Copper</td></tr>
<tr><td>Ethyl Alcohol (EtOH)</td></tr>
<tr><td>Prothrombin Time, INR (PT-INR)</td><td>Haptoglobin</td></tr>
<tr><td>Serology</td><td>Immunoglobulin IgA (Quantitative)</td></tr>
<tr><td>Hepatitis A Virus (HAV) Testing:</td><td>Immunoglobulin IgG (Quantitative)</td></tr>
<tr><td>HAV Total Antibody</td><td>Immunoglobulin IgM (Quantitative)</td></tr>
<tr><td>HAV IgM Antibody</td><td>Phosphatidylethanol (PEth)</td></tr>
<tr><td>Hepatis B Virus (HBV) Testing:</td><td>Urine Chemistry</td></tr>
<tr><td>Hepatitis B surface antigen (HBsAg)</td><td>Drug Screen</td></tr>
<tr><td>Hepatitis B surface antibody (Anti-HBs)</td><td>Ethyl glucuronide (EtG)</td></tr>
<tr><td>Hepatitis B core total antibody (Anti-HBc)</td><td>Other Serology</td></tr>
</table>

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	

[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; no Central Testing available.
[d] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

10.5. Appendix 5: Creatinine Clearance Formula

Note: This formula is to be used for calculating creatinine clearance (CrCl) from **local laboratory results only.**

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85} \text{ (if female), or} \times \mathbf{1.0} \text{ (if male)}}{\mathbf{72} \times \mathbf{serum\ creatinine} \text{ (mg/dL)}}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85} \text{ (if female), or} \times \mathbf{1.0} \text{ (if male)}}{\mathbf{0.81} \times \mathbf{serum\ creatinine} \text{ (μmol/L)}}$$

---

[a] Age in years, weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

10.6. Appendix 6: CTCAE 5.0 Diarrhea/Pneumonitis Definition

Diarrhea/Pneumonitis will be evaluated in this study using the criteria proposed by CTCAE v5.0: 27 November, 2017: 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 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline limiting instrumental ADL	Increase ≥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 or 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 (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					

Abbreviation: ADL = Activities of Daily Living.

10.7. Appendix 7: Inducers and Strong Inhibitors of CYP3A

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

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

Moderate Inducers of CYP3A	
Bosentan	Primidone
Lenisurad	Telotristat ethyl
Modafinil	

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

10.8. Appendix 8: Abbreviations

Term	Definition
ABC	advanced breast cancer
AC	assessment committee
AE	adverse event: Any untoward medical occurrence in a patients or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BID	twice a day, at least 6 hours apart
BM	bowel movement
BUN	blood urea nitrogen
CDK	cyclin-dependent kinase
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CMV	cytomegalovirus
CNS	central nervous system
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.
CR	complete response
CRF	case report form

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
CT	computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
D. Bil	Direct bilirubin
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
DoR	duration of response
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EMA	European Medicine Agency
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EORTC IL36	European Organisation for Research and Treatment of Cancer quality of life questionnaire (abridged)
ERCP	endoscopic retrograde cholangiopancreatography
ET	endocrine therapy
FACT-GP5	Functional Assessment of Cancer Therapy- Side Effects
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GnRH	gonadotropin-releasing hormone
HCRU	healthcare resources used

HDV	hepatitis D virus
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 Committee
IHC	Immunohistochemistry
ILD	Interstitial lung disease
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Interim analysis	An interim analysis is an analysis of clinical 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 Board
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patient allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MBC	metastatic breast cancer
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NRS	numeric pain rating scale

ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PI	package insert
PO	by mouth
PR	partial response
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
PRO-CTCAE	patient reported outcome- Common Terminology Criteria in Adverse Events
PS	performance status
QoL	quality of life
RANK-L	receptor activator of nuclear factor kappa-B ligand
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
SOC	standard of care
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TBL	total bilirubin
TTR	time to response
ULN	upper limit of normal

VTE	venous thromboembolic event

10.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment a: (21-Jun-2019)

This amendment is considered to be 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

Feedback from the FDA regarding inclusion and exlusion criteria, along with clarifications within the protocol, resulted in the need for an amendment.

Section # and Name	Description of Change	Brief Rationale
Throughout protocol	Changed ABC (advanced breast cancer) to MBC (metastatic breast cancer); updated from "advanced" to "metastatic"	Clarification
1.3 Schedule of Activities, 4.3. Justification for Dose, 6.1. Study Intervention(s) Administered	Updated to align sections with inclusion of physician's clinical practice in chemotherapy dose administration	Clarification
1.3 Schedule of Activities, 8.1. Efficacy Assessments	Addition of bodily areas to include in scans, change in frequency in bone scans, updated language regarding tumor assessment frequency to Q12W	Clarification
1.3 Schedule of Activities	Addition of "28 days" to Visit duration for Arm B, related to updates to Section 6.1	Clarification
1.3 Schedule of Activities	Updated language regarding RECIST criteria in the tumor assessments section	
4.1. Overall Design	Clarification of text regarding standard chemotherapy	Clarification
4.2. Scientific Rationale for Study Design	Clarification of text regarding the number of prior ET	Clarification
5.1. Inclusion Criteria	Reduction of calculated creatinine clearance to ≥30mL/min	Based on FDA feedback

Section # and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	Addition of language clarifying that systematic therapy does not include any ET for criteria 15	Clarification
5.2. Exclusion Criteria	Addition of safety language for exclusion criteria 22	Addition
5.4. Screen Failures	Addition of language clarifying rescreening and repeat laboratory testing is allowed once	Clarification
6.1. Study Intervention(s) Administered	Addition of language to dose and schedule row for Arm B	Addition
6.6.3 Dose Suspension and Cycle Delay	Addition of new section discussing cycle delay and dose suspension	Addition
6.5. Concomitant Therapy	Addition of cautionary language to avoid CYP3A strong and moderate inducers	Clarification
6.5. Concomitant Therapy	Deletion of examples of CYP3A inhibitors	Clarification
6.6.1. Abemaciclib	Addition of row to Abemaciclib dose modification and management-diarrhea table regarding Grade 2 CTCAE language; Deletion of Grade 4 row	Addition/Deletion
6.6.2. Fulvestrant and Chemotherapeutic Agents	Addition of language regarding participants being allowed to stay on abemaciclib if fulvestrant is discontinued	Clarification
8.2.1.1. Hepatic Safety Monitoring	Addition of language regarding additional diagnostic testing to rule out cause of increased liver enzymes	Clarification
8.2.1.2. Venous Thromboembolic Events (VTEs)	Addition of language regarding risk language of deep vein thrombosis and pulmonary embolism	Addition
8.2.1.3. Serum Creatinine Increased	Addition of language regarding dose adjustments	Addition

Section # and Name	Description of Change	Brief Rationale
8.2.1.4. Interstitial Lung Disease/Pneumonitis	Addition of language regarding dose adjustments related to ILD/Pneumonitis	Addition
Throughout	Minor editorial and document formatting revisions	These are minor changes; therefore, they have not been summarized.

11. References

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993:85(5):365-376.

Bash E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, Mendoza TR, Hay J, Atkinson TM, Abernethy AP, Bruner DW, Cleeland CS, Sloan JA, Chilukuri R, Baumgartner P, Denicoff A, St Germain D, O'Mara AM, Chen A, Kelaghan J, Bennett AV, Sit L, Rogak L, Barz A, Paul DB, Schrag D. Development of the National Cancer Institute's patient-reported outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JCI: *J Natl Cancer Inst*. 2014; Volume 106(9).

Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, Harbeck N, Aguilar Lopez B, Barrios CH, Bergh J, Biganzoli L, Boers-Doets CB, Cardoso MJ, Carey LA, Cortés J, Curigliano G, Diéras V, El Saghir NS, Eniu A, Fallowfield L, Francis PA, Gelmon K, Johnston SRD, Kaufman B, Koppikar S, Krop IE, Mayer M, Nakigudde G, Offersen BV, Ohno S, Pagani O, Paluch-Shimon S, Penault-Llorca F, Prat A, Rugo HS, Sledge GW, Spence D, Thomssen C, Vorobiof DA, Xu B, Norton L, Winer EP. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Annals of Oncology*. 2018; Vol 29 (8):1634-1657.

CDC Breast Cancer (https://www.cdc.gov/cancer/breast/index.htm) Accessed on: 8 April 2019

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy Scale: development and validation of the general measure. *J Clin Oncol.* 1993; 11:570-579.

Cockcroft DW, Gault MD. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

Cox DR. Regression models and life-tables. *Journal of Royal Statistical Society Ser B*. 1972; 74(2):187-220.

Crawford J, Caserta C, Roila F (on behalf of the ESMO Guidelines Working Group). Hematopoietic growth factors: ESMO recommendations for the applications. *Ann Oncol*. 2009; 20 Suppl 4:162-165.

Di Leo A, O'Shaughnessy J, Sledge GW, Martin M, Lin Y, Frenzel M, Hardebeck MC, Smith IC, Llombart-Cussac A, Goetz MP, Johnston S. Prognostic characteristics in hormone receptor- positive advanced breast cancer and characterization of abemaciclib efficacy. *NPJ Breast Cancer.* 2018;4:41.

Dueck AC, Mendoza TR, Mitchell SA, Reeve BB, Castro KM, Rogak LJ, Atkinson TM, Bennett AV, Denicoff AM, O'Mara AM, Li Y, Clauser SB, Bryant DM, Bearden JD 3rd, Gillis TA, Harness JK, Siegel RD, Paul DB, Cleeland CS, Schrag D, Sloan JA, Abernethy AP, Bruner DW, Minasian LM, Basch E; National Cancer Institute PRO-CTCAE Study Group. Validity and reliability of the US National Cancer Institute's patient-reported outcomes version of the Common Termibology Criteria for Adverse Events (PRO-CTCAE). *JAMA*. 2015;1(8):1051-1059.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd edition). Published by: European Organization for Research and Treatment of Cancer, Brussels 2001.

Flatiron Health EHR-derived database (https://flatiron.com/real-world-evidence/), [02 2019 Dashboard accessed 04April2019]

Flowers CR, Seidenfeld J, Bow EJ, Karten C, Gleason C, Hawley DK, Kuderer NM, Langston AA, Marr KA, Rolston KV, Ramsey SD. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2013;31(6):794-810.

Goetz M, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017; 25(32):3638-3646.

Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes A, Sasano H, Schwartz JN, Sweep FC, Taube S, Torlakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL, Wolff AC. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28(21):3543.

Harbeck N, Gnant M. Breast cancer. *Lancet*. 2017;389(10074):1134-1150.

Leone JP, Leone J, Zwenger AO, Iturbe J, Leone BA, Vallejo CT. Prognostic factors and survival according to tumor subtype in women presenting with breast cancer brain metastases at initial diagnosis. *Eur J Cancer*. 2017 74:17-25.

Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol.* 1997;32(9): 920-924.

Lin P, Hao Y, Xie J, Li N, Zhong Y, Zhou Z, Signorovitch J, Wu E. Physician experiences and preferences in the treatment of HR+/HER2- metastatic breast cancer in the United States: a physician survey. *Cancer Med*. 2016;5(2):209-220.

[NCCN] Gradishar WJ, Anderson BO, Aft R, Balassanian R, Blair SL, Burnstein HJ, Cyr A, Dang C, Elias AD, Farrar WB, Forero A, Giordano SH, Goetz MP, Goldstein LJ, Isakoff SJ, Lyons J, Marcom PK, Mayer IA, McCormick B, Moran MS, O'Regan RM, Patel SA, Pierce LJ, Reed EC, Schwartzberg LS, Sitapati A, Smith KL, Smith ML, Soliman H, Somlo G, Telli ML, Ward JH, Kumar R, Shead DA. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer Version 1.2018- March 20, 2018.

[NCI] National Cancer Institute. Guideline on Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™). Available at:

https://healthcaredelivery.cancer.gov/pro-ctcae/ Published on: 14 Sep 2018. Accessed on: 12 Mar 2019.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655.

Rizzo JD, Somerfield MR, Hagerty KL, Seidenfeld J, Bohlius J, Bennett CL, Cella DF, Djulbegovic B, Goode MJ, Jakubowski AA, Rarick MU, Regan DH, Lichtin AE; American Society of Clinical Oncology; American Society of Hematology. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. *J Clin Oncol.* 2008;26(7):1192.

Rugo HS, Vidula N, Ma C. Improving response to hormone therapy in breast cancer: new targets, new therapeutic options. 2016 ASCO Annual meeting- education session. Presented: 6 June 2016.

Sledge G, Toi M, Neven P, Sohn J, Inoue K, Pivot X, Burdaeva O, Okera M, Masuda N, Kaufman PA, Koh H, Grischke EM, Frenzel M, Lin Y, Barriga S, Smith IC, Bourayou N, Llombart-Cussac A. MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017; 35(25): 2875-2884.

Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leighl NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO; American Society of Clinical Oncology. American Society of Clinical Oncology. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2015;33(28):3199-3212.

Solomayer EF, Diel IJ, Meyberg GC, Gollan C, Bastert G. Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastatis. *Breast Cancer Res Treat*. 2000; 59(3):271-278.

Verzenio package insert. Available at: http://uspl.lilly.com/verzenio/verzenio.html#s1 Published on: Aug 2018. Accessed on 20 Mar 2019.

Waks AG, Winer EP. Breast cancer treament: a review. *JAMA*. 2019;321(3):288-300.

Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P, Hanna W, Jenkins RB, Mangu PB, Paik S, Perez EA, Press MF, Spears PA, Vance GH, Viale G, Hayes DF; American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31(31):3997-4013.

Leo Document ID = 41b4e52f-313f-42b5-b5d6-10097232c7dc

Approver: PPD

Approval Date & Time: 20-Feb-2020 02:32:25 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 20-Feb-2020 12:05:16 GMT

Signature meaning: Approved