Protocol I3Y-MC-JPCP(d)

An Open-Label, Randomized Phase 2 Study of the Impact of Food on Tolerability when Receiving Abemaciclib for Patients with Previously Treated Hormone Receptor-Positive, HER2-Negative, Metastatic Breast Cancer

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Abemaciclib (LY2835219)

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1. Synopsis

Protocol Title:

An Open-Label, Randomized Phase 2 Study of the Impact of Food on Tolerability When Receiving Abemaciclib for Patients with Previously Treated Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer

Rationale:

Abemaciclib is an oral, selective, and potent adenosine triphosphate (ATP)-competitive inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6, respectively). It is currently approved for use in certain geographies as a monotherapy or in combination with hormone therapy for the treatment of patients with advanced or metastatic hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) breast cancer.

MONARCH 1, a single-arm Phase 2 study of abemaciclib 200 mg twice daily (BID) as a single agent in patients with refractory HR+, HER2− metastatic breast cancer (mBC), demonstrated that continuous dosing of single-agent abemaciclib was well tolerated and exhibited promising clinical activity (objective response rate [ORR] of 19.7% (95% confidence interval [CI] 13.3-27.5; 15% not excluded). The most common treatment-emergent adverse events (TEAEs) of any grade were diarrhea (90.2%), fatigue (65.2%), and nausea (64.4%).

MONARCH 2 was a randomized, double-blind Phase 3 study of abemaciclib in combination with fulvestrant in women with HR+, HER2− mBC who had progressed while receiving endocrine therapy. It demonstrated that abemaciclib 150 mg BID plus fulvestrant was effective, with significantly improved progression-free survival (PFS; median 16.4 versus 9.3 months; hazard ratio [HR]=0.553; 95% CI 0.449, 0.681) and in patients with measurable disease an ORR of 48.1% (95% CI 42.6,53.6) compared with 21.3% (95% CI 15.1, 27.6) in the control arm. The most common TEAEs in the abemaciclib versus placebo arms were diarrhea (86.4% versus 24.7%), neutropenia (46.0% versus 4.0%), nausea (45.1% versus 22.9%), and fatigue (39.9% versus 26.9%).

MONARCH 3 was a randomized, double-blind Phase 3 study of abemaciclib in combination with an aromatase inhibitor as initial therapy in women with HR+, HER2− mBC. It demonstrated that abemaciclib 150 mg BID plus a nonsteroidal aromatase inhibitor (NSAI) was effective as initial therapy, significantly improving PFS (median 28.18 versus 14.76 months; HR=0.540; 95% CI 0.418, 0.698); p=.000002). In patients with measurable disease, the ORR was 61% in the abemaciclib arm compared to 45.5% in the placebo arm (p=.003). The most common TEAEs in the abemaciclib versus placebo arms were diarrhea (82.3% versus 32.2%), neutropenia (43.7% versus 32.3%), fatigue (41.3% versus 33.5%), and nausea (41.3% versus 20.5%).

Diarrhea is a frequently associated adverse event (AE) with abemaciclib and has been reported in MONARCH 1, MONARCH 2, and MONARCH 3 studies (Verzenio® United States Package

Insert [USPI]). Diarrhea typically occurs within the first month of treatment and the incidence decreases over the duration of treatment.

Although food can change the bioavailability (BA) of a drug and may have clinically significant consequences, this has not been shown to be the case with abemaciclib. A food effect study has been conducted that evaluated the impact feeding status had on the exposure of abemaciclib. It was demonstrated that a high-fat, high-calorie meal (approximately 800 to 1000 calories with 150 calories from protein, 250 calories from carbohydrate and 500 to 600 calories from fat) administered to healthy subjects increased the area under the concentration versus time curve (AUC) of abemaciclib and its active metabolites by 9% and increased maximum concentration (C_{max}) by 26% (Verzenio® USPI). These changes in exposure were not clinically significant. Currently, abemaciclib is recommended to be taken with or without food (Verzenio® USPI).

In certain circumstances food may mitigate the local gastrointestinal (GI) toxicity of some drugs and this effect may be independent to any relationship between the feeding state and systemic absorption of the drug. To assess if the incidence and severity of the diarrhea associated with abemaciclib may be altered, this study in patients with previously treated HR+, HER2− mBC will evaluate the incidence of dose reductions, dose interruptions, and/or treatment discontinuations due to severe diarrhea (≥Grade 3) or prolonged Grade 2 diarrhea (>7 days duration) when abemaciclib monotherapy is administered (200 mg orally [PO] BID) in the following feeding states; when abemaciclib is taken with a meal, when abemaciclib is taken in the modified fasted condition (defined as at least 1 hour before or 2 hours after a meal), or when abemaciclib is administered without regard to food in patients.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate and summarize incidence of severe diarrhea (≥Grade 3) or prolonged Grade 2 diarrhea (defined as >7 days duration), including the incidence of dose reductions, dose interruptions, and/or treatment discontinuations due to severe diarrhea or prolonged Grade 2 diarrhea over the first 3 cycles when abemaciclib is administered: • with a meal • without a meal, taken in the modified fasted condition • without regard to food	• Incidence of severe diarrhea (≥Grade 3) • Incidence of prolonged Grade 2 diarrhea (defined as >7 days duration) • Dose reductions due to diarrhea • Dose interruptions due to diarrhea • Treatment discontinuations due to diarrhea • Utilization of antidiarrheals
Secondary	
To assess safety and toxicity profile of abemaciclib	The safety endpoints evaluated will include, but are not limited to, the following: • Overall safety • incidence and severity of TEAEs, SAEs, deaths, and clinical laboratory abnormalities
To evaluate PK parameters of abemaciclib and its metabolites	Steady-state concentrations of abemaciclib and its metabolites LSN2839567 and LSN3106726

Abbreviations: PK = pharmacokinetic; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Overall Design:

Study I3Y-MC-JPCP (JPCP) is a multicenter, randomized, open-label Phase 2 study evaluating the impact of food on the incidence of severe diarrhea (≥Grade 3) or prolonged Grade 2 diarrhea (>7 days duration) when receiving abemaciclib monotherapy 200 mg PO BID during the first 3 cycles of study treatment for patients with previously treated HR+, HER2− mBC.

Number of Patients:

The study will screen approximately 100 patients, of whom approximately 60 evaluable patients with HR+, HER2− mBC will be enrolled and randomized 1:1:1 to 1 of the 3 treatment arms as defined by different administration conditions. Randomization will be stratified by region.

Treatment Arms and Duration:

Treatment will be given in an outpatient setting and will continue until the patient is no longer receiving clinical benefit or other discontinuation criteria have been fulfilled. Abemaciclib will be taken on Days 1 to 28 of a 28-day cycle for each treatment arm. The primary outcome phase will consist of the first 3 cycles of treatment. Patients will continue to receive abemaciclib in the extension phase starting with Cycle 4, Day 1. Abemaciclib may be taken without regard to food in the extension phase.

Study Arm	Drug	Dose, mg	Route of Administration	Dose Frequency	Administration Conditions
1	Abemaciclib	200	Oral	BID	Take with a meal
2	Abemaciclib	200	Oral	BID	Take without a meal; at least 1 hour before or 2 hours after a meal (modified fasted condition)
3	Abemaciclib	200	Oral	BID	Take without regard to food

Abbreviation: BID = twice a day.

2. Schedule of Activities

Table JPCP.2.1. Baseline Schedule of Activities

Relative Day Prior to C1D1	≤28	≤14	≤7	Instructions
Procedure				
Informed consent	X			ICF must be signed before any protocol-specific procedures are performed.
Physical exam		X		Include height, weight, and vital signs (temperature, blood pressure, pulse rate, and respiration rate).
ECOG performance status		X		
Medical history		X		Including assessment of preexisting conditions, historical illnesses, substance usage (such as alcohol and tobacco), and other relevant habit assessments.
Current medication		X		Includes 14 days prior to initiation of abemaciclib treatment.
AE collection CTCAE Version 4.0		X		To be reported only after study eligibility is confirmed. See Section 9.2 for reporting expectations.
Radiologic imaging and measurement of palpable or visible lesions	X			Baseline assessments will be done at the investigator's discretion based on the standard of care.
ECG		X		Local ECG.
Hematology		X		Central lab sample collected. Although local sample results can be used for clinical management, a central sample must still be submitted.
Clinical chemistry		X		
Pregnancy test			X	Females of child bearing potential must have a negative serum pregnancy test within 7 days of the first dose of abemaciclib.
Patient diary (e-diary)			X	Dispense e-diary 1 week prior to C1D1 in order to obtain approximately 7 full days of information on number of stools and use of antidiarrheal medication, in order to have a baseline for the patient.

Abbreviations: AE = adverse event; C1D1 = Cycle 1 Day 1; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; e-diary = electronic patient diary; ICF = informed consent form.

Table JPCP.2.2. On-Study-Treatment Schedule of Activities

	Primary Outcome Phase					Extension Phase	30 Day Follow-Up[a]	
	Cycle 1		Cycle 2		Cycle 3	Cycle 4-N	Visit 801	
Day within a Cycle	**1**	**15±1**	**1**	**15±1**	**1**	**1**		
Procedure								**Instructions**
Abemaciclib	X		X		X	X		Take BID on Days 1 through 28 of each cycle.
Physical exam	X		X		X	X	X	Perform prior to dispensing of abemaciclib. Include weight, temperature, blood pressure, pulse rate, respiration rate.
Concomitant medication	X	X	X	X	X	X	X	Throughout study as needed.
AE collection	X	X	X	X	X	X	X	Grading using CTCAE Version 4.0.
ECOG performance status	X		X		X			
Radiologic imaging and measurement of palpable or visible lesions								Efficacy assessments will be done at the investigator's discretion based on the standard of care to confirm eligibility to receive abemaciclib.
ECG								Only perform local additional evaluations in the setting of cardiac symptoms and/or at the discretion of the investigator.
Hematology	X	X	X	X	X	X	X	≤3 days prior to scheduled visit, unless more frequent assessment is clinically indicated; see Appendix 2.
Clinical chemistry	X	X	X	X	X	X	X	
Pharmacokinetics	X	X	X	X	X			For all sample collection details, see Appendix 4.
Patient Diary (e-diary)	X	X	X	X	X			Patients will record daily information on the number of stools, diarrhea, use of loperamide and the timing of the abemaciclib intake relative to their meals

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; e-diary = electronic patient diary; ICF = informed consent form.

[a] Follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the primary outcome or extension phase of the study and lasts approximately 30 days. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

Table JPCP.2.3. Continued-Access Schedule of Activities

	Study Treatment		Follow-Up[a]	Instructions
Cycle			**30-Day Follow-Up**	
Visit	**501**	**502-5XX**	**901**	
Procedure				
Abemaciclib	X	X		Take BID on Days 1 through 28 of each cycle.
AE collection	X	X	X	Grading using CTCAE Version 4.0.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009).

[a] Continued-access follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued-access period and lasts approximately 30 days. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

3. Introduction

3.1. Study Rationale

Abemaciclib is an oral, selective, and potent adenosine triphosphate (ATP)-competitive inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6, respectively). It is currently approved for use in certain geographies as a monotherapy or in combination with hormone therapy for the treatment of patients with advanced or metastatic hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) breast cancer.

MONARCH 1, a single-arm Phase 2 study of abemaciclib 200 mg twice daily (BID) as a single agent in patients with refractory HR+, HER2− metastatic breast cancer (mBC), demonstrated that continuous dosing of single-agent abemaciclib was well tolerated and exhibited promising clinical activity (objective response rate [ORR] of 19.7% (95% confidence interval [CI] 13.3-27.5; 15% not excluded). The most common treatment-emergent adverse events (TEAEs) of any grade were diarrhea (90.2%), fatigue (65.2%), and nausea (64.4%).

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Diarrhea is a frequently associated adverse event (AE) with abemaciclib and has been reported in MONARCH 1, MONARCH 2, and MONARCH 3 studies (Verzenio® United States Package Insert [USPI]; Table JPCP.3.1).

Table JPCP.3.1. Incidence of Diarrhea

Study	Patients N	All Grades (%)	Grade 3 (%)	Grade 4 (%)
MONARCH 1 200 mg PO BID monotherapy	132	90	20	0
MONARCH 2 150 mg PO BID with fulvestrant	441	86	13	0
MONARCH 3 150 mg PO BID with aromatase inhibitor	327	81	9	0

Abbreviations: BID = twice daily; PO = orally.

Diarrhea incidence was greatest during the first month of abemaciclib dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 1, the median time to onset of the first diarrhea event was 7 days and the median duration of diarrhea for Grades 2 and 3 were 7.5 and 4.5 days, respectively.

In MONARCH 3, 19% of patients with diarrhea required a dose omission and 17% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. In MONARCH 1, 26% of patients with diarrhea required a dose omission and 23% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 1, MONARCH 2, and MONARCH 3 studies.

Diarrhea typically occurs within the first month of treatment and the incidence decreases over the duration of treatment. It is predictable and manageable with over-the-counter medications. The supportive diarrhea management guidelines (Sections 7.2.1 and 7.7.1) incorporated in the MONARCH study protocols, including early use of antidiarrheal agents and dose adjustments, appeared to have been effective in limiting the recurrence, duration, and severity of diarrhea. The majority of diarrhea events recovered or resolved and the rate of discontinuation due to diarrhea was low. In MONARCH 1 (Figure JPCP.3.1), the incidence of diarrhea reduced by end of Cycle 3, with no Grade 3 and 10.6% Grade 2 events.

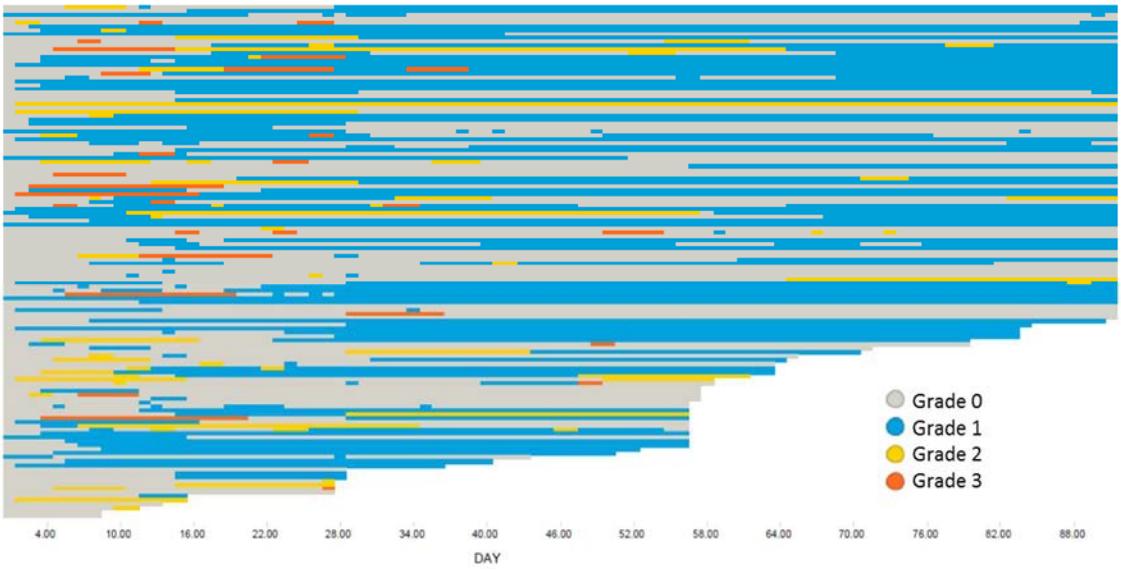

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Figure JPCP.3.1. Analysis of treatment-emergent adverse event of diarrhea in MONARCH 1.

Although food can change the bioavailability (BA) of a drug and may have clinically significant consequences, this has not been shown to be the case with abemaciclib. A food effect study has been conducted that evaluated the impact feeding status had on the exposure of abemaciclib. It was demonstrated that a high-fat, high-calorie meal (approximately 800 to 1000 calories, with 150 calories from protein, 250 calories from carbohydrate and 500 to 600 calories from fat) administered to healthy subjects increased the area under the concentration versus time curve (AUC) of abemaciclib and its active metabolites by 9% and increased maximum concentration (C_{max}) by 26%. (Verzenio® USPI). These changes in exposure were not clinically significant. Currently, abemaciclib is recommended to be taken with or without food (Verzenio® USPI).

In certain circumstances food may mitigate the local gastrointestinal (GI) toxicity of some drugs and this effect may be independent to any relationship between the feeding state and systemic absorption of the drug. To assess if the incidence and severity of the diarrhea associated with abemaciclib may be altered, this study in patients with previously treated HR+, HER2− mBC will evaluate the incidence of dose reductions, dose interruptions, and/or treatment discontinuations due to severe diarrhea (≥Grade 3) or prolonged Grade 2 diarrhea (>7 days duration) when abemaciclib monotherapy is administered (200 mg orally [PO] BID) in the following feeding states; when abemaciclib is taken with a meal, when abemaciclib is taken in the modified fasted condition (defined as at least 1 hour before or 2 hours after a meal), or when abemaciclib is administered without regard to food in patients.

3.1.1. Background

Abemaciclib is an oral, selective, and potent ATP-competitive inhibitor of CDK4 and CDK6. CDK4 and CDK6 promote cell growth by facilitating the progression of cells from the G1 to the

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

Continuously dosed abemaciclib has demonstrated single-agent clinical activity in both the I3Y-MC-JPBA (JPBA) Phase 1b study, with a response rate of 33.3% across dose levels, and the I3Y-MC-JPBN (JPBN; MONARCH 1) Phase 2 study, with a response rate of 19.7% (at 200-mg dose BID), in patients with heavily pretreated HR+ mBC that is refractory to endocrine therapy (Patnaik et al. 2016; Dickler et al. 2017). Additionally, abemaciclib plus endocrine therapy resulted in statistically significant improvements in both PFS and response rate in HR+, HER2− advanced breast cancer in patients who progressed on or following endocrine therapy (I3Y-MC-JPBL [JPBL; MONARCH 2]) and in patients receiving first-line treatment (I3Y-MC-JPBM [JPBM; MONARCH 3]).

Abemaciclib has an acceptable safety profile in the respective patient populations studied in the 2 Phase 3 trials (MONARCH 2 and MONARCH 3) in combination with endocrine therapy and the Phase 2 study (MONARCH 1), a monotherapy study. The safety monitoring and corresponding dose adjustment guidelines used in these clinical studies effectively improved the tolerability profile of abemaciclib. Abemaciclib was approved in the United States for use in the treatment of HR+, HER2− mBC based on the above referenced clinical studies.

3.2. Benefit/Risk Assessment

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

4. Objectives and Endpoints

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

Table JPCP.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate and summarize incidence of severe diarrhea (≥Grade 3) or prolonged Grade 2 diarrhea (defined as >7 days duration), including the incidence of dose reductions, dose interruptions, and/or treatment discontinuations due to severe diarrhea or prolonged Grade 2 diarrhea over the first 3 cycles when abemaciclib is administered: • with a meal • without a meal, taken in the modified fasted condition • without regard to food	• Incidence of severe diarrhea (≥Grade 3) • Incidence of prolonged Grade 2 diarrhea (defined as >7 days duration) • Dose reductions due to diarrhea • Dose interruptions due to diarrhea • Treatment discontinuations due to diarrhea • Utilization of antidiarrheals
Secondary	
To assess safety and toxicity profile of abemaciclib	The safety endpoints evaluated will include, but are not limited to, the following: • Overall safety • incidence and severity of TEAEs, SAEs, deaths, and clinical laboratory abnormalities
To evaluate the PK parameters of abemaciclib and its metabolites	Steady-state concentrations of abemaciclib and its metabolites LSN2839567 and LSN3106726

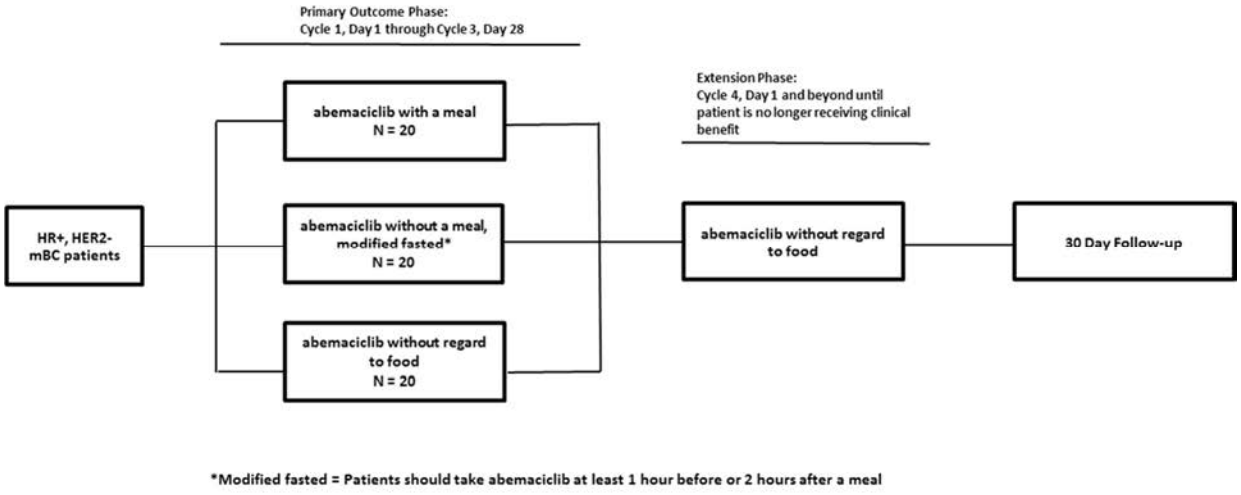
Abbreviations: PK = pharmacokinetic; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

5. Study Design

5.1. Overall Design

Study I3Y-MC-JPCP (JPCP) is a multicenter, randomized, open-label Phase 2 study evaluating the impact of food on the incidence of severe diarrhea (≥Grade 3) or prolonged Grade 2 diarrhea (>7 days duration) when receiving abemaciclib monotherapy 200 mg PO BID during the first 3 cycles of study treatment for patients with previously treated HR+, HER2− mBC. Randomization will be 1:1:1 to the 3 food administration conditions, and randomization will be stratified by region.

Figure JPCP.5.1 illustrates the study design.



Abbreviations: HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; mBC = metastatic breast cancer; N = number of patients.

Figure JPCP.5.1. Illustration of study design.

5.2. Number of Patients

The study will screen approximately 100 patients, of whom approximately 60 evaluable patients with HR+, HER2− mBC will be enrolled and randomized 1:1:1 to 1 of the 3 treatment arms as defined by different administration conditions. Randomization will be stratified by region.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

Refer to Figure JPCP.7.1 for a depiction of study completion, the continued-access period, and end of study.

5.4. Scientific Rationale for Study Design

Refer to Section 3.1.

5.5. Justification for Dose

As the incidence of reported diarrhea was greatest in MONARCH 1 for both overall grades and Grade 3, this study will enroll patients who are deemed suitable by their physician for treatment with abemaciclib monotherapy at the recommended dose of 200 mg orally BID.

6. Study Population

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

6.1. Inclusion Criteria

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

[1] have a diagnosis of HR+, HER2− mBC

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

[2] have all of the following:

- Recurrent, locally advanced, unresectable or mBC
- Prior treatment with disease progression following anti-estrogen therapy for locally advanced or metastatic disease
- Prior treatment with at least one chemotherapy regimen for locally advanced or metastatic disease. Patients are eligible if they discontinue chemotherapy prior to demonstrating disease progression
- No prior treatment with CDK4 and CDK6 inhibitor

[3] have the presence of measurable or nonmeasurable disease as determined by investigator.

[4] are of an acceptable age to provide informed consent according to the local regulations and are at least 18 years of age, male or female (regardless of menopausal status).

[5] have a performance status (PS) of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al. 1982)

[6] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures, including keeping records in the electronic patient diary (e-diary) as required by study protocol.

[7] have discontinued all previous treatments for cancer and recovered from the acute effects of therapy. All patients who experienced diarrhea as a side effect of previous therapy must have recovered to ≤Grade 1 prior to enrollment. Patients must have discontinued from previous treatments, as shown below:

Previous Treatment	**Length of Time Prior to First Dose of Study Treatment**
Cytotoxic therapies	≥21 days
Targeted agents (small-molecule inhibitors)	≥5 half-lives or ≥28 days, whichever is shorter
Hormonal therapy	≥21 days
Biologic agents (other than immunotherapy)	≥21 days
Limited field radiotherapy for palliative intent	≥14 days
Other radiotherapy	≥28 days
Major surgery	≥14 days
Immunotherapy	≥21 days

[8] have adequate organ function, as defined below:

System	**Laboratory Value**
Hematologic	
ANC	≥1.5×10^9 cells/L. Note: G-CSF should not be administered to meet ANC eligibility criterion.
Platelets	≥100×10^9/L
Hemoglobin Transfusions to increase the patient's hemoglobin level to 8 g/dL are permitted; however, study treatment must not begin until at least 1 day after the transfusion.	≥8 g/dL
Hepatic	
Total bilirubin[a]	≤1.5×ULN
ALT and AST	≤3×ULN
Renal	
Serum creatinine	≤1.5×ULN

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

[a] Gilberts syndrome with a total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are eligible.

[9] men with partners of child-bearing potential or women of child-bearing potential must agree to use a medically approved contraceptive method during and for at least 3 weeks following the last dose of abemaciclib (eg, intrauterine device [IUD], nonhormonal birth control pills, or barrier method). If condoms are used as a barrier contraceptive, a spermicidal agent should be added as double barrier protection.

[10] women of child-bearing potential must have a negative pregnancy test documented within 7 days prior to treatment.

[11] have an estimated life expectancy that will permit the patient to complete 3 cycles of treatment.

[12] are able to swallow tablets/capsules.

[13] have given written informed consent prior to any study-specific procedures (refer to Appendix 3, Study Governance, Regulatory, and Ethical Considerations).

6.2. Exclusion Criteria

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

[14] are currently receiving treatment in a clinical study involving an investigational product or are enrolled into any other type of medical research judged not to be scientifically or medically compatible with this study.

[15] have a serious concomitant systemic disorder (for example, active infection or a GI disorder causing clinically significant symptoms such as nausea, vomiting or diarrhea [such as Crohn's disease, ulcerative colitis], or profound immune suppression) or a serious preexisting medical condition (for example, history of major surgical resection involving the stomach or small bowel) that, in the opinion of the investigator, would compromise/preclude the patient's ability to adhere to the protocol.

[16] have symptomatic central nervous system (CNS) malignancy or metastasis (screening not required).

Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids (discontinued steroids at least 7 days prior to study treatment initiation) and/or anticonvulsants and their disease is asymptomatic and radiologically stable for at least 30 days.

[17] have a symptomatic human immunodeficiency virus (HIV) infection or symptomatic activated/reactivated hepatitis A, B, or C (screening is not required).

[18] have a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest. Exceptions are:

- patients with ablated Wolfe Parkinson White are eligible

- patients with controlled atrial fibrillation for >30 days prior to randomization are eligible.

[19] have a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years.

[20] had major surgery within 14 days prior to randomization to allow for post-operative healing of the surgical wound. Note: a surgery qualifies as major per investigators/surgeon judgement based on the required recovery period, both from general patient status and post-operative healing perspective.

[21] are breastfeeding.

[22] have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days of the initial dose of study drug for a nonmyelosuppressive or myelosuppressive agent, respectively.

6.3. Lifestyle Restrictions

This is a lifestyle restriction study examining the relationship between timing of food and administration of abemaciclib, evaluating its impact on severe diarrhea (≥Grade 3) or prolonged Grade 2 diarrhea (>7 days duration); see Sections 7.1 and 7.6, administration conditions and defined adherence.

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

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Individuals may be re-screened up to 1 time. The interval between re-screenings should be at least 2 weeks. When re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

Repeating of laboratory tests during the screening period does not constitute re-screening.

7. Treatments

7.1. Treatments Administered

Abemaciclib monotherapy will be administered 200 mg PO BID with specific administration conditions. Patients will be instructed to take their daily doses of abemaciclib either with a meal, without a meal in a modified fasting state (defined as at least 1 hour prior to or 2 hours after a meal), or without regard to food for the first 3 cycles. Patients will be requested to record the abemaciclib dosing and administration conditions followed in a diary. Abemaciclib will be taken on Days 1 to 28 of a 28-day cycle for each treatment arm. Table JPCP.7.1 shows the treatment regimens.

Patients will be instructed to commence loperamide at the first sign of loose stools and thereafter as per local label. See Section 7.7.1.1 for supportive management guidance. Patients will be required to record loperamide dose and frequency in a diary. Loperamide will be supplied or reimbursed by the sponsor according to local laws. If additional antidiarrheals are prescribed by the physician, they should be entered on the concomitant medication CRF.

Table JPCP.7.1. Treatment Administration

Study Arm	Drug	Dose, mg	Route of Administration	Dose Frequency	Administration Conditions
1	Abemaciclib	200	Oral	BID	Take with a meal
2	Abemaciclib	200	Oral	BID	Take without a meal; at least 1 hour before or 2 hours after a meal (modified fasted condition)
3	Abemaciclib	200	Oral	BID	Take without regard to food

Abbreviation: BID = twice a day.

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

- explaining the correct use of the drug and planned duration of each individual's treatment to the patient/study-site personnel/legal representative.
- verifying that instructions are followed properly the first 3 cycles. Abemaciclib is taken as per the assigned study arm outlined in Table JPCP.7.1.
- maintaining accurate records of abemaciclib dispensing and collection.
- returning all unused medication to Lilly, or its designee at the end of the study, unless the site is authorized by Lilly or its designee to destroy unused medication, as allowed by local law.
- educating the patient on the management of diarrhea as per Section 7.7.1.1.

7.1.1. Packaging and Labelling

Abemaciclib will be provided by Lilly and will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomly assigned to 1 of the 3 treatment arms. Assignment to treatment arms will be determined by a computer-generated random sequence using an interactive Web-response system (IWRS). Randomization will be stratified by region.

7.2.1. Selection and Timing of Doses

During the on-study treatment period (primary outcome phase and extension phase), a delay of study treatment due to holiday, weekend, inclement weather, or other unforeseen circumstances will be permitted for a maximum of 7 consecutive days and not counted as a protocol deviation. In exceptional cases, for planned delays (including, but not limited to vacation or holidays), additional study treatment may be dispensed. In these cases, patients should return to the original visit schedule calculated from Day 1.

For each study arm, abemaciclib will be administered orally at 200 mg BID, with at least 6 hours separating doses on a continuous schedule and as assigned by administration conditions for each study arm. Details on treatment administration are described in Section 7.1. Treatment with abemaciclib will be given until evidence of disease recurrence or other discontinuation criteria are met (see Section 8).

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

7.4.1. Special Treatment Considerations of Adverse Events of Special Interest

Table JPCP.7.2 presents dose adjustments to occur IF the event was related to abemaciclib. Any questions related to **dose adjustments** may be discussed with Lilly CRP.

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

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose reduction is NOT required.
Hematologic Toxicity	Recurrent[a] Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic Toxicity	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic Toxicity: **If patient requires administration of blood cell growth factors**	Regardless of severity (Use of growth factors according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level unless already performed for incidence of toxicity that led to the use of growth factor.
Non-Hematologic Toxicity[b] (except diarrhea, ALT increased, and ILD/pneumonitis)	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1.	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Non-Hematologic Toxicity[b] (except diarrhea, ALT increased, and ILD/pneumonitis)	Grade 3 and 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea	Grade 2 that does not resolve within 24 hours to at least Grade 1	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose reduction is NOT required.
Diarrhea	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures, or any Grade of diarrhea that requires hospitalization	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT Increased[c]	Persistent or recurrent[a] Grade 2 (>3.0-5.0×ULN), or Grade 3 (>5,0-20.0×ULN)[c]	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.

ALT Increased[c]	Grade 4 (>20.0×ULN)	Abemaciclib therapy **MUST** be discontinued.	Abemaciclib therapy **MUST** be discontinued.
ALT Increased[c] with increased total bilirubin, in the absence of cholestasis	Grade 3 increased ALT (>5.0 x ULN) with total bilirubin >2 x ULN	Abemaciclib therapy **MUST** be discontinued	Abemaciclib therapy **MUST** be discontinued
ILD/Pneumonitis[b]	Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days	Dose **MUST** be suspended until toxicity resolves to baseline or Grade ≤1	Dose **MUST** be reduced by 1 dose level.
ILD/Pneumonitis[b]	Grade 3 or 4	Abemaciclib therapy MUST be discontinued	Abemaciclib therapy MUST be discontinued

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

Note: MUST = mandatory.

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

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

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

b Additional guidance for hepatic monitoring, renal, and ILD/pneumonitis is provided in Sections 9.4.2.1, 9.4.2.2, and 9.4.2.4.

c Grade 3 ALT increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 9.4.2.1 for additional guidance for hepatic monitoring.

7.4.1.1. Dose Adjustments of Abemaciclib

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

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

Table JPCP.7.3. Dose Adjustments of Abemaciclib

Dose Adjustment	Oral Dose	Frequency
0	200 mg	Twice daily with at least 6 hours between doses
1	150 mg	Twice daily with at least 6 hours between doses
2	100 mg	Twice daily with at least 6 hours between doses
3	50 mg	Twice daily with at least 6 hours between doses

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

7.4.1.2. Dose Delays and Omission of Abemaciclib

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

Study treatment may be held up to 28 days to permit sufficient time for recovery from the toxicity.

Patients not recovering from toxicity within 28 days should be considered for discontinuation of study treatment. In exceptional circumstances, a delay >28 days is permitted upon agreement between the investigator and the Lilly CRP and abemaciclib dose adjustment is to be considered.

Patients undergoing surgery should have abemaciclib suspended. For minor surgeries and procedures (eg, ambulatory), consultation with the Lilly CRP is not required. For major surgeries, the recommendation is to suspend dosing of abemaciclib for at least 7 days before, and for up to 14 days after, the procedure. Consider monitoring neutrophils and platelets before surgery and before resuming abemaciclib. The scars should be aseptic and healing process reasonable before resuming abemaciclib. This is all monitored to prevent infection and hemorrhagic and/or healing complications. For minor surgeries, investigators should treat as clinically indicated and closely monitor any signs of infection or healing complications.

All patients who require palliative radiation should have their treatment held. This must be discussed and agreed with Lilly CRP; see Section 7.7.

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

7.5. Preparation/Handling/Storage/Accountability

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

7.6. Treatment Compliance

Patient compliance with study medication and completion of patient e- diary will be assessed at each visit. Compliance will be assessed by counting returned tablets/capsules and e-diary review. The e-diary will be supplied by Lilly. Deviations from the prescribed dosage regimen should be recorded on the case report form (CRF). Patients who are deemed noncompliant will

receive additional training, as required, and the importance of compliance with the protocol will be reinforced.

Patients who are significantly noncompliant with abemaciclib and administration conditions may be discontinued from abemaciclib treatment after discussion/consultation with the Lilly CRP. A patient will be considered noncompliant or if she/he misses more than 25% of abemaciclib doses during the first 3 cycles of treatment. Similarly, a patient will be considered significantly noncompliant if she or he is judged by the investigator to have intentionally or repeatedly taken more than (≥125%) the prescribed amount of medication. Abemaciclib dose suspensions or delays related to toxicity may occur and will not result in a patient being considered as noncompliant.

7.7. Concomitant Therapy

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

No other anticancer therapy will be permitted while patients are on study treatment. Of note, megestrol acetate as an appetite stimulant is permitted.

Concurrent treatment with standard-of-care bone-modifying agents (such as bisphosphonates or receptor activator of nuclear factor kappa B ligand [RANKL]-targeting agents) is permitted.

Abemaciclib is extensively metabolized through oxidation by cytochrome P450 (CYP)3A. 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 6).

All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated. Patients requiring more than 7 days of dexamethasone therapy will not incur a protocol deviation.

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

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

No other chemotherapy, immunotherapy, cancer-related hormone therapy, experimental drugs, or herbal supplements intended to treat cancer will be permitted while the patients are on this study.

Palliative radiation therapy is permitted after discussion with and agreement of the Lilly CRP or designee for irradiating small areas of painful metastases that cannot be managed adequately using systemic or local analgesics. Such areas must not be an identified target lesion if Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 is used to measure disease 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.

7.7.1. Supportive Care

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

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

7.7.1.1. Supportive Management for Diarrhea

Patients should receive instructions on the management of diarrhea and prescribed antidiarrheal therapy (protocol recommended loperamide) on Day 1. The antidiarrheal agent, loperamide is not for prophylactic use, and should only be used in the event of diarrhea. Loperamide will be supplied or reimbursed by the sponsor according to local laws. In the event of diarrhea, provided loperamide antidiarrheal therapy should be initiated as early as possible and the site should follow the guidance below:

- At the first sign of loose stools, the patient should initiate loperamide antidiarrheal therapy, if not already receiving such therapy, and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with loperamide therapy within 24 hours to either baseline or Grade 1, abemaciclib should be suspended until diarrhea is resolved to baseline or Grade 1.
- When abemaciclib recommences, dosing should be adjusted as outlined in Table JPCP.7.2 and Section 7.4.1.1.

In cases of significant diarrhea, Grades 2 through 4 (Appendix 7), that have not responded to interventions as outlined above, if the investigators are considering the addition of steroids to treat potential colitis, the sponsor strongly recommends an endoscopic procedure to document colitis prior to initiating steroids.

In cases of severe 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 [IV] rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

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

7.7.1.2. Therapy for Febrile Neutropenia

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

7.7.1.3. Growth Factor Therapy

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

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

7.8. Treatment after the End of the Study

Not applicable.

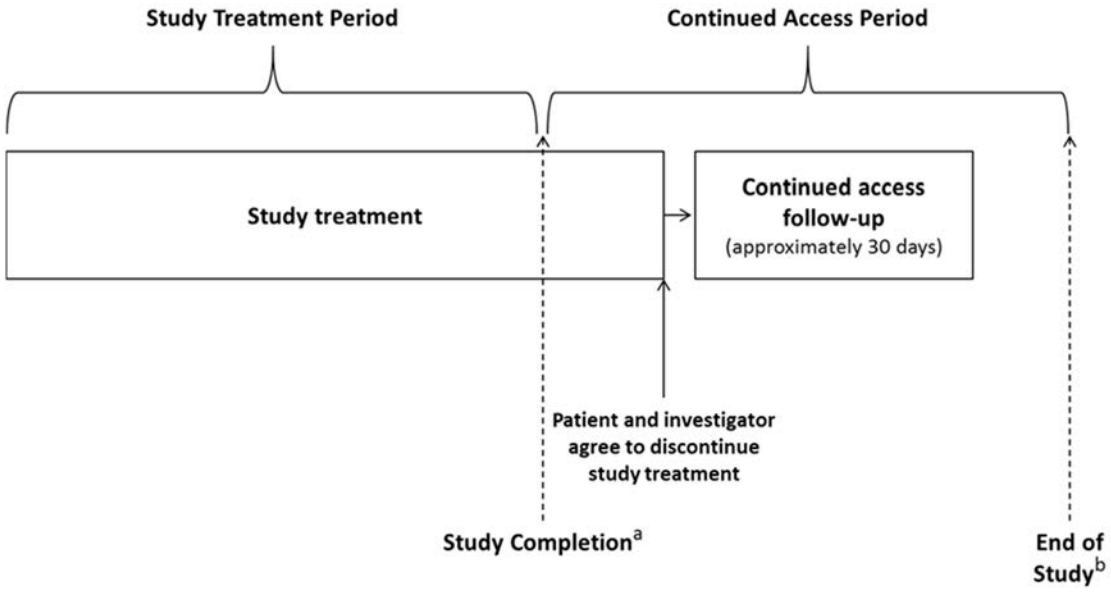
7.8.1. Treatment after Study Completion

Study completion will occur when the last enrolled patient completes up to Cycle 4 Day 1. Investigators will continue to follow the Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred.

7.8.1.1. Continued Access

The continued-access period will apply to this study only if at least 1 patient is still on abemaciclib when study completion occurs.

Patients who are still on abemaciclib at the time of study completion may continue to receive abemaciclib in the continued-access period if they are experiencing clinical benefit and no undue risks.



[a] Lilly will notify sites when study completion occurs.
[b] End of study occurs at the last visit or last scheduled procedure for the last patient.

Figure JPCP.7.1. Continued-access diagram.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

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

- the patient is treated in any other clinical study involving an investigational product or enrolled into any other type of medical research judged not to be scientifically or medically compatible with this study
- the patient becomes pregnant during the study
- the patient is significantly noncompliant with study procedures and/or treatment as described in Section 7.6
- the patient has evidence of disease progression
- the patient experiences unacceptable toxicity
- the patient has had 3 dose reductions and experiences an AE that would cause a fourth dose reduction
- the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from abemaciclib will occur prior to introduction of the new agent
- the investigator decides that the patient should be discontinued from abemaciclib
- the patient requests to be discontinued from abemaciclib.

Patients who are discontinued from abemaciclib will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If Lilly or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without abemaciclib. Patients who are discontinued from abemaciclib will have safety follow-up procedures performed as shown in the Schedule of Activities (Section 2).

8.2. Discontinuation from the Study

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

- 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)
- the investigator decides that the patient should be discontinued from the study

- the patient requests to be withdrawn from the study
- the patient's legal representative requests that the patient be discontinued from the study
- the study has been completed as defined in Section 5.3.

Patients who are discontinued from the study will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Lost to Follow-Up

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

9. Study Assessments and Procedures

Section 2 provides the Schedule of Activities for this study.

Appendix 2 provides a list of the laboratory tests that will be performed for this study.

Appendix 4 provides the schedule for collection of samples in this study.

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

9.1. Efficacy Assessments

Efficacy assessments are not applicable in this study. However, the investigator is required to confirm that the patient is still deriving benefit from study treatment and has no evidence of disease progression.

9.1.1. Electronic Patient Diary Assessment

Electronic patient diary (e-diary) assessment will collect number of bowel movements and diarrhea, thereby increasing the validity of measures reported by the patient and minimizing transcription errors in recording the measures. The use of e-diaries should also allow more frequent and timely interactions between investigator and patients. The system will be used to collect timing of abemaciclib doses taken relative to the time of their closest meal. Additionally, the e-diary system will incorporate reminders for patients to complete their diary.

Physicians and designated clinical staff will have access to the e-diary portal (secure web-based site) with the ongoing near real-time updating of patient reported diarrhea. Manual inspection of data will support patient safety monitoring, as well as the potential for reaching an optimum diarrhea management. Investigative staff can assess clinical data via the e-diary portal and recommend on dosing adjustments.

An instruction manual will be provided to patients and investigative sites. Additional instruction and training will be provided to the investigative sites regarding data collection, review, retention and archival processes. In the event of e-diary malfunction or loss, the patient will be instructed to immediately contact the investigative site for instructions regarding replacement of the equipment.

9.2. Adverse Events

The investigator will use Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (NCI 2009) to assign severity grades.

Investigators are responsible for:

- monitoring the safety of patients who have entered into 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 appropriate medical care of patients during the study
- documenting their review of each laboratory safety report
- following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to study treatment or the study, or that caused the patient to discontinue abemaciclib before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

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

After the ICF is signed, study site personnel will record via electronic data entry 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, study site personnel will record via electronic data entry any change in the preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to abemaciclib and/or study procedure via electronic data entry.

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

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

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

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

- important medical events that may not be immediately life-threatening or result in death or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above.

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

Study site personnel must notify Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Lilly approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

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

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient 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.

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

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

9.2.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study treatment or study procedure. United States 21 CFR 312.32 and Regulation (EU) No. 536/2014 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.

9.2.3. Complaint Handling

Lilly collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, to 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.

9.3. Treatment of Overdose

Refer to the IB, Section 7.3.9.

9.4. Safety

9.4.1. Safety Measures

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

Any clinically significant findings that result in a diagnosis and that occur after the patient receives the first dose of abemaciclib should be reported to Lilly or its designee as an AE via electronic data entry. Refer to Section 9.2 for details on the recording of AEs.

9.4.2. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

Refer to Section 9.4.2.1 for details regarding hepatic safety data collection in the event of particular circumstances.

9.4.2.1. Special Hepatic Safety Data Collection

If a study patient experiences elevated ALT≥5×ULN and elevated TBL≥2×ULN, or ALT≥8×ULN, liver tests (Appendix 5), including ALT, AST, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests (Appendix 5) and in consultation with the Lilly CRP. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels. Additional diagnostic testing should be considered to rule out cause of increased liver enzymes per the investigator's discretion

Hepatic data (Appendix 5) should be collected in the event that 1 or more of the following conditions is met for the patient during the course of the study:

- ALT≥5×ULN and TBL≥2×ULN
- ALT≥8×ULN
- discontinuation from study treatment due to a hepatic event or an abnormality of liver tests

9.4.2.2. Safety Monitoring: Renal Function

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C-calculated glomerular filtration rate.

Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function.

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

A serum cystatin C will be collected with the central chemistry laboratory sample.

9.4.2.3. Safety Monitoring: Venous Thromboembolic Events

In the randomized Phase 3 studies in breast cancer patients who received abemaciclib in combination with endocrine therapy, there was a greater number of patients 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 studies with single-agent abemaciclib use in the mBC population or other tumor types, 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. Monitor patients for signs and symptoms of deep vein thrombosis and pulmonary embolism and treat as medically appropriate.

9.4.2.4. Safety Monitoring: Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis has been identified as an adverse drug reaction for abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2 with serious cases and fatal events reported. Additional information is available in the IB.

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

Refer to Table JPCP.7.2 for guidance on dose adjustments of abemaciclib for patients with ILD/pneumonitis (see Appendix 7 for CTCAE grades). Discontinue abemaciclib in cases of severe ILD/pneumonitis.

9.4.2.5. Diarrhea Safety Data Collection

Diarrhea events will be collected in an e-diary. If the patient experiences diarrhea, the patient should record this in the e-diary, including the potential use of loperamide. The patient should contact the site as necessary. Reports of diarrhea will be graded according to CTCAE

version 4.0 by the investigator based upon data collected in e-diary and in consultation with the patient. All episodes of diarrhea must be reported as (S)AEs via electronic data entry.

9.5. Pharmacokinetics

Pharmacokinetic (PK) samples will be collected as shown in Section 2 and Appendix 4. Blood samples will be used to determine the concentrations of abemaciclib and metabolites LSN2839567 and LSN3106726.

A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon by the investigator and Lilly.

Bioanalytical samples collected to measure abemaciclib concentration and metabolism and/or protein binding will be retained for a maximum of 2 years following the last patient visit for the study.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics

Not applicable.

9.8. Biomarkers

Not applicable.

9.9. Health Economics

Health economics and medical resource utilization parameters will not be evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

The primary objective of this study is to evaluate the impact of 3 different meal settings on the incidence of severe diarrhea (≥Grade 3) or prolonged Grade 2 diarrhea (>7 days duration) as well as dose reductions, dose interruptions, and treatment discontinuations due to diarrhea, and utilization of antidiarrheals for patients receiving abemaciclib monotherapy. This study will enroll up to approximately 100 patients to obtain approximately 20 patients who complete the primary outcome phase per meal administration condition. Randomization will be 1:1:1 to the 3 administration conditions and randomization will be stratified by region. The sample size is based on regulatory guidance, not statistical powering.

10.2. Populations for Analyses

The following analysis sets will be defined for this study:

Intention-to-treat (ITT) analysis set: 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 analyses and patient dispositions.

Per-protocol analysis set: will include all randomized patients who receive at least 1 dose of abemaciclib and do not have any major protocol violations that could potentially affect the conclusions of the study, such as significant noncompliance with meal administration conditions or abemaciclib administration. This analysis set will be used for sensitivity analyses related to the primary objective.

Safety analysis set: 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 cohort assignment. The safety analysis set will be used for analyses related to the primary objective and for all dosing/exposure and safety analyses.

Pharmacokinetic analysis set: will include all enrolled patients who received at least 1 dose of abemaciclib and have at least 1 postbaseline evaluable PK sample and evaluable dosing information.

10.3. Statistical Analyses

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

No hypothesis tests are planned for this study. The analysis of this study will be descriptive only, except for possible exploratory analyses as deemed appropriate. Parameter estimates, including CIs, if relevant, and summary statistics will be reported. Unless otherwise stated, all CIs will be given at a 2-sided 95% level. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages. Missing data will not be imputed.

Analyses related to the primary objective, safety analyses, and other analyses will be summarized by treatment arm for the primary outcome phase (first 3 cycles). In addition, analyses may be repeated by combining all patients in the safety population and summarizing data for the primary outcome phase and extension phase combined.

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

10.3.1. Analyses Related to the Primary Objective

The primary analysis will evaluate each meal administration condition group for measures related to diarrhea in the first 3 cycles using the safety analysis set. Secondary analyses will be repeated using the per-protocol population.

- Incidence of severe diarrhea (≥Grade 3)
- Incidence of prolonged Grade 2 diarrhea (defined as >7 days duration)
- Dose reductions due to diarrhea
- Dose interruptions due to diarrhea
- Treatment discontinuations due to diarrhea
- Utilization of antidiarrheals.

10.3.2. Safety Analyses

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

The Medical Dictionary for Regulatory Activities (MedDRA®) Version 21.0 (or higher) will be used when reporting AEs by MedDRA terms. The MedDRA Lower Level Term (LLT) will be used in the treatment-emergent computation. Treatment-emergent AEs will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term (PT) within SOC.

Safety analyses will include summaries of the following:

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

10.3.3. Other Analyses

10.3.3.1. Patient Disposition

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

10.3.3.2. 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.

10.3.3.3. Treatment Compliance

The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity for the first 3 cycles will be summarized for all treated patients by treatment arm.

Study treatment compliance 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 tablets/capsules dispensed and returned over the course of the first 3 cycles.

Compliance to the administration condition will be assessed as the proportion of doses during the first 3 cycles of treatment that are taken during the meal window allowed by the assigned administration condition. For each dose of abemaciclib taken during the first 3 cycles, the patient will record the administration condition in a diary.

10.3.3.4. Concomitant Therapy

A summary of prior and concomitant medications will be reported.

10.3.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic analyses will be conducted on all patients who have received at least 1 dose of abemaciclib and have evaluable PK samples and sufficient dosing information.

Mean population PK parameters for abemaciclib (and metabolites, if warranted) in plasma (for example, clearance, exposure, volume of distribution) and inter-individual PK variability will be computed using nonlinear mixed-effect modeling (NONMEM). Steady-state exposures for each individual will be calculated based on the available dosing and concentration information using the previously developed population PK model.

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

Furthermore, pharmacodynamic data (such as, time to first diarrhea event or severity of first diarrhea event) collected in this study may also be analyzed by means of NONMEM and connected to the population PK model in a pharmacokinetic/pharmacodynamics (PK/PD) model.

11. References

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	Adverse event: any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-versus-time curve
CAP	College of American Pathologists
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum concentration
CNS	central nervous system
CPK	creatine phosphokinase
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.
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DVT	deep venous thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

end of study	Date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.
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.
ER	estrogen receptor
ERB	ethical review board
EU	European Union
GCP	good clinical practice
G-CSF	granulocyte-colony-stimulating factor
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation (formerly the International Conference on Harmonisation)
IHC	immunohistochemistry
ILD	interstitial lung disease
interim analysis	An analysis of clinical study data conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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 patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IUD	intrauterine device
IV	intravenous
IWRS	interactive Web-response system
LLT	MedDRA Lower-Level Term
Lilly	Eli Lilly and Company
MATE	multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
NONMEM	nonlinear mixed-effect modeling
PE	pulmonary embolism
PFS	progression-free survival
PK	pharmacokinetic(s)
PK/PD	Pharmacokinetic/
PS	performance status
PT	MedDRA Preferred Term
randomize	The process of assigning patients to an experimental group on a random basis.
Rb	retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study.
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
screen failure	A patient who does not meet 1 or more criteria required for participation in a study.

SOC	MedDRA System Organ Class
study completion	Occurs when the last enrolled patient completes up to Cycle 4 Day 1, as determined by Lilly.
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent at baseline, or worsens relative to the baseline state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
VTE	venous thromboembolic event

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology – laboratory[a]	**Local**	**Central**
Leukocytes (WBC)		X
Neutrophils[b]		X
Lymphocytes		X
Monocytes		X
Eosinophils		X
Basophils		X
Erythrocytes (RBC)		X
Hemoglobin (HGB)		X
Hematocrit (HCT)		X
Mean corpuscular volume (MCV)		X
Mean corpuscular hemoglobin concentration (MCHC)		X
Platelets (PLT)		X
Clinical Chemistry – laboratory	**Local**	**Central**
Serum Concentrations of:		
Alanine aminotransferase (ALT)		X
Albumin		X
Alkaline phosphatase		X
Aspartate aminotransferase (AST)		X
Bilirubin, direct		X
Bilirubin, total		X
Blood urea nitrogen (BUN) or blood urea		X
Calcium		X
Cholesterol		X
Creatinine		X
Cystatin C		X
Glucose, nonfasting		X
Magnesium		X
Potassium		X
Sodium		X
Pregnancy Test (for female patients of child-bearing potential) - laboratory	**Local**	**Central**
Serum pregnancy test	X	

Abbreviations: CRF = case report form; RBC = red blood cells; WBC = white blood cells.

[a] Treatment decisions can be based on local laboratory results.

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

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient/patient's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that the patient's participation is voluntary
- ensuring that informed consent is given by each patient/patient's legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study procedures and prior to the administration of abemaciclib.
- providing a copy of the signed ICF(s) to the patient/patient's legal representative and retaining a copy of the signed ICF in the site file
- answering any questions the patient/patient's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's/patient's legal representative's willingness to continue the patient's participation in the study.

Ethical Review

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

Regulatory Considerations

This study will be conducted in accordance with the protocol and with:

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

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

Investigator Information

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

Protocol Signatures

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

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

Final Report Signature

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

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

Data Quality Assurance

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

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

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

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

Data Capture System

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

An electronic data capture system 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

sponsor-provided electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

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

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports 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.

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Sampling Schedule

Pharmacokinetic samples should be taken at the same time as the hematology and clinical chemistry samples. In the appropriate forms, record date and time of the sample, and the date and time of the dose that was taken prior to the PK sample.

Sampling Schedule for Pharmacokinetics

	Cycle 1		Cycle 2		Cycle 3
Procedure	Day 1	Day 15	Day 1	Day 15	Day 1
Pharmacokinetics	Prior to the first dose	In conjunction with other laboratory samples	In conjunction with other laboratory samples		In conjunction with other laboratory samples

Note: PK Sampling may be done at same time as hematology and clinical chemistry labs (+/- 1 day on Cycle 1 Day 15 and Cycle 2 Day 15 per Section 2 Schedule of Activities)

Appendix 5. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin (HGB)	
Hematocrit (HCT)	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time (PT)
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets (PLT)	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
Alanine aminotransferase (ALT)	**Recommended Autoimmune Serology**
Aspartate aminotransferase (AST)	Anti-nuclear antibody[a]
Gamma-glutamyl transferase (GGT)	Anti-smooth muscle antibody[a]
Creatine phosphokinase (CPK)	Anti-actin antibody[a]

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

[a] Assayed by Lilly-designated laboratory.

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

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

Appendix 6. Protocol JPCP Inducers and Inhibitors of CYP3A

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

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

Moderate Inducers of CYP3A
Bosentan
Lenisurad
Modafinil
Primidone
Telotristat ethyl

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

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

Appendix 7. Protocol JPCP CTCAE 4.03 Definitions

Diarrhea will be evaluated in this study using the criteria proposed by CTCAE v4.0 revised: CTCAE 4.03–June 14, 2010: Gastrointestinal disorders.

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

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

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

Appendix 8. Protocol JPCP: ECOG Performance Status

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

Appendix 9. Protocol I3Y-MC-JPCP Amendment (d) An Open-Label, Randomized Phase 2 Study of the Impact of Food on Tolerability when Receiving Abemaciclib for Patients with Previously Treated Hormone Receptor-Positive, HER2-Negative, Metastatic Breast Cancer Summary

Overview

Study I3Y-MC-JPCP(d), an open-label, randomized Phase 2 study of the impact of food on tolerability when receiving abemaciclib for patients with previously treated hormone receptor-positive, HER2-negative, metastatic breast cancer, has been amended. The new protocol is indicated by amendment (d) and will be used to conduct the study in place of any preceding version.

- Table JPCP.7.2 was updated to include dose modification and delay guidance for interstitial lung disease (ILD)/pneumonitis events that aligns with the updated Investigator's Brochure.
- Section 7.7. was updated to align with the updated Investigator's Brochure
- To cluster all special safety monitoring guidance under Section 9.4.2. Safety Monitoring:
    - Section 9.4.3. was changed to Section 9.4.2.2.
    - Section 9.4.4. was changed to Section 9.4.2.3.
    - Section 9.4.5. was changed to Section 9.4.2.4.
    - Section 9.4.6. was changed to Section 9.4.2.5.
- Section 9.4.2.4 was updated to align with the updated Investigator's Brochure.
- Appendix 1 was updated to include interstitial lung disease (ILD).
- Appendix 6was updated to align with changes made in Section 7.7 and to include moderate inducers and additional stronginhibitors of CYP3A.

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

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

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

Non-Hematologic Toxicity[b] (except diarrhea, ~~and~~ ALT increased, and ILD/pneumonitis)	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1.	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Non-Hematologic Toxicity[b] (except diarrhea, ~~and~~ ALT increased, and ILD/pneumonitis)	Grade 3 and 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
ILD/Pneumonitis[b]	Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days	Dose **MUST** be suspended until toxicity resolves to baseline or Grade ≤1	Dose **MUST** be reduced by 1 dose level.
ILD/Pneumonitis[b]	Grade 3 or 4	Abemaciclib therapy MUST be discontinued	Abemaciclib therapy MUST be discontinued

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

b Additional guidance for ~~renal~~ hepatic monitoring, renal ~~hepatic monitoring~~, and ILD/pneumonitis is provided in Sections 9.4.2.1, 9.4.2.2, and 9.4.2.4.

Section 7.7. Concomitant Therapy

All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated. Patients requiring more than 7 days of dexamethasone therapy will not incur a protocol deviation

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

~~The results from in vitro studies in cultured human hepatocytes indicate that abemaciclib and its major metabolites, LSN2839567 and LSN3106726, downregulate mRNA of CYPs, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A, at clinically relevant concentrations. The mechanism of mRNA downregulation and its clinical relevance are not yet understood. Therefore, care should be taken when coadministering substrate drugs of the above~~

~~CYPs with narrow therapeutic margin (Appendix 6). The information in Appendix 6 is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.~~

~~9.4.3~~ 9.4.2.2 Safety Monitoring: Renal Function

~~9.4.4~~ 9.4.2.3 Safety Monitoring: Venous Thromboembolic Events

~~9.4.5~~ 9.4.2.4 Safety Monitoring: Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis has been identified as an adverse drug reaction for abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2 with serious cases and fatal events reported. Additional information is available in the IB.

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

~~Interstitial lung disease (ILD)/pneumonitis has been identified as an adverse drug reaction for abemaciclib. The majority of events observed in the abemaciclib clinical trial program were Grade 1 or Grade 2 with serious cases and fatal events reported. Additional information is available in the IB.~~

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

~~For patients who develop radiological changes suggestive of ILD/pneumonitis and have few or no symptoms (Grade 1), no dose modifications are required. For ≥Grade 3 or persistent or recurrent Grade 2 ILD/pneumonitis events, abemaciclib should be suspended until toxicity resolves to baseline or Grade 1, and resumed at the next lower dose.~~

Refer to Table JPCP.7.2 for guidance on dose adjustments of abemaciclib for patients with ILD/pneumonitis (see Appendix 7 for CTCAE grades). Discontinue abemaciclib in cases of severe ILD/pneumonitis.

~~9.4.6~~ 9.4.2.5 Diarrhea Safety Data Collection

Appendix 1. Abbreviations and Definitions:

ILD	interstitial lung disease

Appendix 6. Protocol JPCP Inducers and Inhibitors of CYP3A ~~or Substrates of CYPs with Narrow Therapeutic Range~~

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

~~Inducers of CYP3A~~
~~Carbamazepine~~
~~Dexamethasone[a]~~
~~Phenobarbital/phenobarbitone~~
~~Phenytoin~~
~~Rifapentine~~
~~Rifampin~~
~~Rifabutin~~
~~St John's wort~~

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

~~Strong Inhibitors of CYP3A~~
~~Aprepitant~~
~~Ciprofloxacin~~
~~Clarithromycin~~
~~Diltiazem~~
~~Erythromycin~~
~~Fluconazole~~
~~Itraconazole~~
~~Ketoconazole~~
~~Nefazodone~~
~~Verapamil~~

~~**Cytochrome P450 Substrates with Narrow Therapeutic Range**~~

~~Cytochrome P450~~	~~Substrate~~
~~CYP1A2~~	~~Theophylline~~ ~~Tizanidine~~
~~CYP2C9~~	~~Warfarin~~ ~~Phenytoin~~
~~CYP2D6~~	~~Thioridazine~~ ~~Pimozide~~
~~CYP3A~~	~~Alfentanil~~ ~~Astemizole~~ ~~Cisapride~~ ~~Cyclosporine~~

	~~Dihydroergotamine~~ ~~Ergotamine~~ ~~Fentanyl~~ ~~Pimozide~~ ~~Quinidine~~ ~~Sirolimus~~ ~~Tacrolimus~~ ~~Terfenadine~~

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

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

Moderate Inducers of CYP3A
Bosentan
Lenisurad
Modafinil
Primidone
Telotristat ethyl

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

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

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