I3Y-MC-JPCB Protocol (d)

Effects of Multiple Doses of Abemaciclib on the Pharmacokinetics of Cytochrome P450 (CYP) 1A2, CYP2C9, CYP2D6, and CYP3A Substrates (Caffeine, Warfarin, Dextromethorphan, and Midazolam) in Cancer Patients

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Approval Date: 22-Sep-2016

1. Protocol I3Y-MC-JPCB(d)

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Confidential Information

Abemaciclib (LY2835219)

This Phase 1 study is an open-label, 4-period, fixed-sequence study to investigate the effect of abemaciclib on pharmacokinetics of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), dextromethorphan (CYP2D6 substrate), and midazolam (CYP3A substrate) in patients with advanced and/or metastatic cancer, followed by a safety extension phase.

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Protocol Electronically Signed and Approved by Lilly: 06 October 2015.
Amendment (a) Electronically Signed and Approved by Lilly: 21 December 2015
Amendment (b) Electronically Signed and Approved by Lilly: 25 January 2016
Amendment (c) Electronically Signed and Approved by Lilly: 24 March 2016

Amendment (d) Electronically Signed and Approved by Lilly
on approval date provided below.

Approval Date: 22-Sep-2016 GMT

2. Synopsis

Oncology Protocol Synopsis: Study I3Y-MC-JPCB

Name of Investigational Product: Abemaciclib (LY2835219)	
Title of Study: Effects of Multiple Doses of Abemaciclib on the Pharmacokinetics of Cytochrome P450 (CYP) 1A2, CYP2C9, CYP2D6, and CYP3A Substrates (Caffeine, Warfarin, Dextromethorphan, and Midazolam) in Cancer Patients	
Number of Planned Patients: Up to 48 patients may be enrolled in order that 22 patients complete Periods 1 and 2.	**Phase of Development:** 1
Length of Study: Screening: Up to 30 days Period 1: 7 days Period 2: 12 days Periods 3 & 4: 16 & 28 days, respectively Safety extension: Patients are allowed to continue receiving abemaciclib in 28-day cycles until disease progression or other reason for discontinuation per investigator's assessment.	
Objectives: The primary objective of this study is to assess the effect of abemaciclib on the pharmacokinetics (PK) of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), dextromethorphan (CYP2D6 substrate), and midazolam (CYP3A substrate) in cancer patients after multiple oral doses of abemaciclib. The secondary objectives of this study are: • to characterize the tolerability of coadministration of abemaciclib with caffeine, warfarin, dextromethorphan, and midazolam following multiple doses of abemaciclib in cancer patients. • to assess the effect of abemaciclib on blood pressure and pulse rate following multiple doses of abemaciclib in cancer patients. The exploratory objectives of this study are: • to determine the effect of abemaciclib on the pharmacodynamics (PD) of a single dose of warfarin as measured by international normalized ratio (INR). • to assess the effect of abemaciclib on markers of renal function, including creatinine, cystatin-C, kidney injury molecule-1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL). • to characterize bowel habits via a patient diary and a stool assessment tool (Bristol Stool Chart). • to characterize diarrhea experienced via patient reported outcome data based on selected individual items from existing patient reported outcomes (PRO) scales (FACIT-D) as well as custom-generated PRO items.	
Study Design: This will be an open-label, four-period, fixed-sequence study, followed by a safety extension phase, in patients with advanced and/or metastatic cancer. The drug cocktail of 100 mg caffeine, 10 mg warfarin, 30 mg dextromethorphan, and 0.2 mg midazolam will be administered orally as a single dose on 2 occasions: Day 1 in Period 1, and in combination with abemaciclib on Day 8 of Period 2, after 7 days of 200 mg abemaciclib every 12 hours (Q12H) dosing. After completing Period 2, patients will continue to receive abemaciclib at a dose of 200 mg Q12H (or a modified dose) through the end of Periods 3 and 4, in 28-day cycles, and then may continue in a safety extension phase until discontinuation criteria are met.	

Diagnosis and Main Criteria for Inclusion and Exclusion:

Patients may be included in the study if they meet the following criteria: have histological or cytological evidence of a diagnosis of cancer that is advanced and/or metastatic; are ≥18 years of age; have adequate organ function; have a performance status of ≤2 on the Eastern Cooperative Oncology Group (ECOG) scale; and have discontinued all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, cancer-related hormone therapy, and investigational therapy) for at least 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents prior to receiving study drug and have recovered from the acute effects of therapy (treatment related toxicity resolved to baseline), except for residual alopecia.

Investigational Product, Dosage, and Mode of Administration:

Abemaciclib

Abemaciclib will be supplied as 50-mg capsules as the 25% w/w formulation (C3) for oral administration.

Drug Cocktail

This will include: commercially available caffeine citrate solution (20 mg/mL) for oral administration; commercially available warfarin (brand name Coumadin) as 5-mg tablets for oral administration; commercially available dextromethorphan as 15-mg liquid gel capsules for oral administration; and commercially available midazolam syrup (2 mg/mL) for oral administration.

Planned Duration of Treatment:

Period 1

On Day 1, 10 mL of 20-mg/mL caffeine citrate solution, 2 × 5-mg tablets of warfarin, 2 × 15-mg liquid gel capsules of dextromethorphan, and 0.1 mL of 2-mg/mL midazolam syrup will be coadministered

Period 2

On Days 1 to 12, 4 × 50-mg capsule of abemaciclib will be administered orally in the morning and evening. On Day 8, abemaciclib will be coadministered with 10 mL of 20 mg/mL caffeine citrate solution, 2 × 5-mg tablets of warfarin, 2 × 15-mg liquid gel capsules of dextromethorphan, and 0.1 mL of 2-mg/mL midazolam syrup.

Periods 3, 4, and Safety Extension Phase

Patients receive an abemaciclib dose of 200 mg Q12H (or modified dose as applicable) on a 28-day cycle until discontinuation criteria are met.

Criteria for Evaluation:

Safety: Adverse events (AEs), clinical laboratory evaluations, vital signs, ambulatory blood pressure monitoring (ABPM), electrocardiograms (ECGs), bowel habits, renal function markers, and CYP genotyping.

Bioanalytical: Plasma concentrations of caffeine, S-warfarin, dextromethorphan, midazolam, and abemaciclib.

Pharmacokinetic: The primary parameters for analysis will be maximum observed drug concentration (C_{max}), area under the concentration versus time curve from zero to infinity (AUC[0-∞]), and time of maximum observed drug concentration (t_{max}).

Efficacy: Tumor assessments.

Evaluation Methods:

Safety: Safety data will be listed and summarized as appropriate.

Pharmacokinetic: Pharmacokinetic parameter estimates will be evaluated to delineate effects of drug interaction. Caffeine, warfarin, dextromethorphan, and midazolam administered in the absence of abemaciclib will represent the reference treatments and be analyzed separately. Each drug administered with abemaciclib will represent the test treatments. Log-transformed C_{max} and AUC(0-∞) estimates will be evaluated in a linear mixed-effects analysis of variance model with a fixed effect for treatment and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding confidence intervals (90% CIs).

The t_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, 90% CIs, and p-values from the Wilcoxon test will be calculated.

Trough plasma concentrations of abemaciclib will be listed.

3. Table of Contents

Effects of Multiple Doses of Abemaciclib on the Pharmacokinetics of Cytochrome P450 (CYP) 1A2, CYP2C9, CYP2D6, and CYP3A Substrates (Caffeine, Warfarin, Dextromethorphan, and Midazolam) in Cancer Patients

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Attachments

Attachment **Page**

4. Abbreviations and Definitions

Term	Definition
ABPM	ambulatory blood pressure monitoring
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from zero to infinity
AUC(0-t_{last})	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC_{INR}	area under the INR curve
audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
CDK	cyclin-dependent kinase
CI	confidence interval
C_{max}	maximum observed drug concentration
CNS	central nervous system
complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CRF/eCRF	case report form/electronic case report form: Sometimes referred to as clinical report form, a printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CP	clinical pharmacologist
CRP	clinical research physician
CRS	clinical research scientist
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least one dose of study treatment.
enter	Patients who are entered in the trial are those who have signed the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board/institutional review board: A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
ESA	erythroid-stimulating agents
GCP	good clinical practice
IB	Investigator's Brochure
IC_{50}	50% inhibition concentration
ICF	informed consent form
ICH	International Conference on Harmonization
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

INR	international normalized ratio
INR_{max}	maximum observed INR response
interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for datalock.
investigational product (IP)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial. Investigational product includes a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the authorized form, used for an unauthorized indication or used to gain further information about the authorized form
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
KIM-1	kidney injury molecule-1
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NGAL	neutrophil gelatinase-associated lipocalin
NSCLC	non-small-cell lung cancer
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participants are aware of the drug therapy received during the study.
patient	A subject with a defined disease.
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRO	patient reported outcomes
Q12H	every 12 hours
RECIST	Response Evaluation Criteria in Solid Tumors
re-screen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.

screen failure	A patient who does not meet one or more criteria required for participation in a trial
sponsor	The party who takes responsibility for the initiation, management and/or financing of a clinical study.
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life associated with the terminal rate constant
TEAE	treatment-emergent adverse event
t_{max}	time of maximal plasma concentration
TPO	third-party organization
ULN	upper limit of normal

Effects of Multiple Doses of Abemaciclib on the Pharmacokinetics of Cytochrome P450 (CYP) 1A2, CYP2C9, CYP2D6, and CYP3A Substrates (Caffeine, Warfarin, Dextromethorphan, and Midazolam) in Cancer Patients

5. Introduction

5.1. Rationale and Justification for the Study

Study JPCB is a Phase 1 study designed to investigate the effect of multiple doses of abemaciclib on the pharmacokinetics (PK) of cytochrome P450 (CYP) 1A2, CYP2C9, CYP2D6, and CYP3A substrates in patients with advanced and/or metastatic cancer.

Abemaciclib is an orally administered small molecule that is a potent and selective dual inhibitor of the cyclin-dependent kinases (CDKs) 4 and 6. The goal of inhibiting CDK4 and CDK6 is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

Abemaciclib at doses of 200 mg every 12 hours (Q12H) is being developed for the treatment of advanced cancer, including metastatic breast cancer and Stage IV non-small-cell lung cancer.

Abemaciclib has been administered orally on Days 1 through 28 of a 28-day cycle. In Study JPBA, the maximum tolerated dose for humans when administered as a single agent was 200 mg Q12H. Based upon a higher incidence of Grade 3 diarrhea when abemaciclib 200 mg Q12H was administered in combination with nonsteroidal aromatase inhibitors, the dose being explored in combination with nonsteroidal aromatase inhibitors in Study JPBM is 150 mg Q12H.

In vitro in human liver microsomes, abemaciclib and its major circulating metabolites LSN2839567 (M2) and LSN3106726 (M20) did not inhibit directly or in a time-dependent manner the catalytic activities of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A at clinically relevant concentrations. Furthermore, abemaciclib and its metabolites did not induce the catalytic activities of CYP1A2, CYP2B6, and CYP3A. Thus, collectively, these in vitro data suggest that abemaciclib and its metabolites do not interact directly with the above CYPs, and that drug interactions are unlikely due to CYP inhibition or induction when abemaciclib is coadministered with substrate drugs of the above CYPs.

Although abemaciclib and its major metabolites did not inhibit any of the CYPs directly in human liver microsomes, down regulation of mRNA of CYPs, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A by abemaciclib and/or its major circulating metabolites LSN2839567 (M2) and LSN3106726 (M20), was observed at clinically relevant concentrations in cultured human hepatocytes. The observed mRNA down regulation was >50%, concentration dependent and not due to toxicity to cells. The mechanism of this down regulation and its clinical relevance (in vitro to in vivo correlation) are presently not understood. Thus, in the absence of additional in vitro data there is a potential for abemaciclib and its major metabolites to interact with substrate drugs of the above CYPs when coadministered (EMA Guidance 2012; PMDA Draft Guidance 2013).

Under this circumstance, regulatory agencies recommend conducting a clinical drug interaction study using a cocktail approach (EMA Guideline 2012; PMDA Draft Guideline 2013). Drugs used in such a cocktail should be selective for the specific CYP enzymes, should not interact with each other, and ultimately should be safe when administered. One such cocktail is a modified Coopertown 5 + 1 cocktail which includes caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6) and midazolam (CYP3A), and has been administered to patients with advanced cancers (excluding primary liver tumors) (Goh et al. 2010; Ma et al. 2006). In this study, based on the in vitro data, only caffeine, warfarin, dextromethorphan, and midazolam will be included in the cocktail.

Secondary and exploratory objectives of this study are to collect closely-monitored data on blood pressure, diarrhea, and renal function that will further characterize the safety and tolerability of abemaciclib in patients.

The sponsor, monitor, and investigators will perform this study in compliance with the protocol, good clinical practice (GCP) and International Conference on Harmonization (ICH) guidelines, and applicable regulatory requirements.

5.2. Objectives

5.2.1. Primary Objective

The primary objective of this study is to assess the effect of abemaciclib on the PK of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), dextromethorphan (CYP2D6 substrate), and midazolam (CYP3A substrate) in cancer patients after multiple oral doses of abemaciclib.

5.2.2. Secondary Objectives

The secondary objectives of this study are:

- to characterize the tolerability of coadministration of abemaciclib with caffeine, warfarin, dextromethorphan, and midazolam following multiple doses of abemaciclib in cancer patients.
- to assess the effect of abemaciclib on blood pressure and pulse rate following multiple doses of abemaciclib in cancer patients.

5.2.3. Exploratory Objectives

The exploratory objectives of this study are:

- to determine the effect of abemaciclib on the pharmacodynamics (PD) of a single dose of warfarin as measured by international normalized ratio (INR).
- to assess the effect of abemaciclib on markers of renal function, including creatinine, cystatin-C, kidney injury molecule-1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL).
- to characterize bowel habits via a patient diary and a stool assessment tool (Bristol Stool Chart).

- to characterize diarrhea experienced via patient reported outcome data based on selected individual items from existing patient reported outcomes (PRO) scales (FACIT-D) as well as custom-generated PRO items.

5.3. General Introduction to Abemaciclib

Abemaciclib is a selective and potent small molecule CDK4 and CDK6 dual inhibitor with broad antitumor activity in preclinical pharmacology models, acceptable physical and PK properties, and an acceptable toxicity profile in nonclinical species. This compound demonstrates significant inhibition of tumor growth as monotherapy in multiple human xenograft models including models for: colorectal cancer, glioblastoma multiforme, acute myeloid leukemia, melanoma, mantle cell lymphoma, and non-small-cell lung cancer (NSCLC).

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

5.3.1. Clinical Experience with Abemaciclib

Abemaciclib has been evaluated in multiple Phase 1 clinical pharmacology studies, including 4 studies completed in healthy subjects and 2 studies completed in cancer patients. Three Phase 1 studies are ongoing in healthy subjects and several Phase 1 studies are underway in cancer patients.

Phase 2 studies are ongoing in metastatic breast cancer and mantle cell lymphoma patients and Phase 3 studies are ongoing in patients with metastatic breast cancer and in patients with Stage IV NSCLC.

5.3.1.1. Pharmacokinetics of Abemaciclib and Its Major Metabolites

The time course of abemaciclib concentration in plasma shows a median time of maximum observed drug concentration (t_{max}) ranging from 4 to 6 hours postdose. Abemaciclib has a half-life associated with the terminal rate constant ($t_{1/2}$) ranging from 17 to 38 hours and showed no dose dependent change in clearance. The time to steady state following multiple Q12H doses of abemaciclib is approximately 5 days.

Based on in vitro data, the major human circulating metabolites LSN3106726 (M20) and LSN2839567 (M2) are active with potency similar to abemaciclib. The $t_{1/2}$ was longer for metabolites than that of abemaciclib, with mean values of 36 and 32 hours for M2 and M20, respectively.

Additional information on the PK properties of abemaciclib, including the PK at steady state after repeated abemaciclib administration, is available in the IB. The majority of abemaciclib is

eliminated in feces (81%) with approximately 3% of the dose eliminated in urine. Abemaciclib is extensively metabolized primarily via CYP3A.

5.3.1.2. Clinical Activity Data

Abemaciclib has demonstrated evidence of clinical activity in several tumor types. In Study JPBA, radiographic responses were achieved in previously treated patients with breast cancer, NSCLC, and melanoma. For hormone receptor-positive breast cancer, overall response rate was 31% (11/36 patients) and disease control rate was 81% (29/36 patients).

5.3.1.3. Clinical Safety Data

Safety data for 352 patients treated with abemaciclib in 6 studies show that the most common treatment-emergent AEs (TEAEs; ≥10%) possibly related to study drug for patients receiving abemaciclib either as a single agent, with endocrine therapy, or with chemotherapy, are diarrhea (64.2%), nausea (44.3%), fatigue (39.8%), neutropenia (27.0%), vomiting (24.1%), thrombocytopenia (21.3%), leukopenia (21.0%), anemia (17.6%), decreased appetite (17.6%), and increased blood creatinine (14.5%). The majority of deaths reported for patients in the studies with available safety data were due to study disease.

Preliminary safety data from Study JPBH, a Phase 1b study evaluating the safety and tolerability of abemaciclib in combination with endocrine therapies (including anastrozole) in patients with HR+, HER2- mBC, have shown an AE profile for abemaciclib administered at 200 mg every 12 hours in combination with endocrine therapies that is consistent with the profile observed in the Study JPBA mBC single agent cohort. However, at the 200-mg dose, the incidence of treatment-emergent Grade 3 diarrhea was greater in combination with endocrine therapies than when abemaciclib was administered alone (25.7% and 13.6%, respectively). Although diarrhea occurred in 62.5% of patients in the dose-confirmation phase of Study JPBA (57.1% of patients at the 150-mg dose and 68.0% of patients at the 200-mg dose), this diarrhea was mostly Grade 1 or Grade 2 and was manageable with standard anti-diarrheal agents. There have been no patient discontinuations due to diarrhea.

In one study, a total of 16 patients were taking warfarin while also taking abemaciclib: one patient each at abemaciclib doses of 100 mg Q12H and 225 mg daily, 6 patients at 200 mg Q12H, and 8 patients at 150 mg Q12H. Two patients in this group of 16 patients had an AE potentially related to increased warfarin exposure that could potentially occur if CYP2C9 activity was decreased. One patient had Grade 1 epistaxis and an increased INR on Day 28 of the study while taking a dose of 200 mg abemaciclib Q12H. One patient had a Grade 3 upper gastrointestinal hemorrhage on Day 179 of the study while taking a dose of 150 mg abemaciclib Q12H.Increases in serum creatinine of approximately 20% to 40% above baseline have been observed across healthy subject and cancer patient studies. In vitro preliminary data from transporter inhibition studies have shown that abemaciclib and its major metabolites inhibit multiple drug and toxin extrusion transporter 1. Thus, the observed transient increases in serum creatinine are likely to be due to inhibition of tubular secretion of creatinine by this transporter without clinically meaningful alterations in renal function (Schützer et al. 2010; Imamura et al. 2011; Lepist et al. 2014).

Changes in blood pressure and pulse rates have been seen in studies with abemaciclib. In healthy subjects enrolled in Study JPBG, small decreases in mean blood pressure and increases in mean pulse rates were observed up to 24 hours following dosing with abemaciclib in each study period. Maximal mean changes were up to -5.0 mmHg for systolic blood pressure and -4.3 mmHg for diastolic blood pressure, and up to 4.3 bpm increases in pulse rate. In cancer patients enrolled in Study JPBA, decreases in blood pressure were observed following dosing with abemaciclib on Days 8, 15, 22, and 28 of Cycle 1 and Day 28 of Cycles 2 through 6. Maximal median changes were up to -6 mmHg for diastolic blood pressure (Cycle 1 Day 28) and -5 mmHg for systolic blood pressure (Cycle 1 Day 22). Decreases from baseline in pulse rate were observed on Days 15 and 22 of Cycle 1, as well as on Day 28 of Cycles 3 through 6, with maximal median change in pulse rate being -6.0 bpm (Cycle 6 Day 28). To date there is no evidence of an effect of abemaciclib on QT interval.

5.3.2. Nonclinical Toxicology

To support human clinical studies, the toxicity profile of abemaciclib has been effectively characterized in rat and dog through a package of repeat-dose toxicology, safety pharmacology, and genetic toxicology studies. These studies demonstrate an acceptable safety profile with toxicities that are generally considered to be monitorable and reversible.

The nonclinical toxicology studies consisted of 28-day repeat-dose studies in rats at doses of 10, 30, and 50 mg/kg/day (60, 180, and 300 mg/m^2, respectively) and in dogs at doses of 1, 3, and 10 mg/kg/day (20, 60, and 200 mg/m^2, respectively). Dose-responsive hematotoxicity, indicated by cytopenias and bone marrow hypocellularity, and gastrointestinal injury were the most prominent adverse effects observed in both rats and dogs. In addition, effects on male reproductive tract were also observed. These changes were generally consistent with antiproliferative effects and demonstrated partial or complete reversibility within the 28-day recovery period in both species. Importantly, the toxicities associated with abemaciclib in preclinical studies have generally been observed with multiple or repeated dosing, consistent with its cell cycle-related mechanism of action.

No important compound-related findings were observed in safety pharmacology studies of the cardiovascular system, respiratory system, or central nervous system (CNS) in preclinical studies. Although the 50% inhibition concentration (IC_{50}) was not precisely determined in an in vitro model (IC_{50} >1.65 μM), no QTc prolongation was observed in dogs at doses up to 10 mg/kg; therefore, the risk for QTc prolongation to occur in humans is considered low.

For more details about the results of the nonclinical toxicology studies, please refer to Section 5.2.1 of the IB.

5.4. Rationale for Selection of Dose

A drug cocktail containing oral doses of 2 mg/kg caffeine, 10 mg warfarin, 40 mg omeprazole, 30 mg dextromethorphan, and 0.075 mg/kg midazolam has been studied previously (Ma et al. 2006), with no safety concerns raised. Another study evaluating this cocktail of drugs in patients with advanced cancer also had no safety concerns raised (Goh et al. 2010). Therefore, the drug

cocktail proposed in the current study, which contains 100 mg caffeine, 10 mg warfarin, 30 mg dextromethorphan, and 0.2 mg midazolam, is expected to be safe and well tolerated.

Abemaciclib

A dose of 200 mg Q12H was selected for this study and is supported by the safety data from a cancer patient study in which the highest dose explored was 275 mg Q12H, and the maximum tolerated dose was identified as 200 mg Q12H based on dose-limiting toxicity of Grade 3 fatigue observed in 2 of 3 patients at 275 mg Q12H. Likewise, the 200-mg dose is supported by safety data from healthy subject studies. The available nonclinical toxicology data also supports the dose selected for this study. The 200-mg dose is also being investigated in the Phase 2 and Phase 3 single agent studies of abemaciclib in cancer patients.

At the conclusion of the drug interaction portion of the study, patients may continue to receive abemaciclib through Cycle 2 at the investigator's discretion. In the safety extension phase, patients will receive abemaciclib at a dose of 200 mg Q12H (or modified as applicable) on a 28-day cycle until discontinuation criteria are met.

6. Investigational Plan

6.1. Study Population

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

6.1.1. Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria during screening prior to enrollment.

[1] Have histological or cytological evidence of a diagnosis of cancer that is advanced and/or metastatic. The patient must be, in the judgment of the investigator, an appropriate candidate for experimental therapy after available standard therapies have failed to provide clinical benefit for their disease.

[2] Are ≥18 years of age.

[3] Have given written informed consent prior to any study-specific procedures.

[4] Have adequate organ function, including:

- Hematologic: Absolute neutrophil count ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, and hemoglobin ≥8 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin until 1 day after the erythrocyte transfusion.
- Hepatic: Direct bilirubin ≤1.5 times upper limits of normal (ULN), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤2.5 times ULN. PT or INR ≤1.2 times ULN and PTT≤1.2 times ULN.
- Renal: Serum creatinine no greater than ULN.

[5] Have other clinical laboratory test results within normal reference range or results with acceptable deviations that are judged to be not clinically significant by the investigator.

[6] Have a performance status of ≤2 on the Eastern Cooperative Oncology Group (ECOG) scale (refer to Attachment 5).

[7] Have discontinued all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, cancer-related hormone therapy, and investigational therapy) for at least 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents prior to receiving study drug and have recovered from the acute effects of therapy (treatment related toxicity resolved to baseline), except for residual alopecia.

At the discretion of the investigator, hormone refractory prostate cancer patients who are stable on gonadotropin-releasing hormone agonist therapy may have that treatment continued while they are enrolled in Study JPCB. Other hormonal treatments used for non-cancer indications (or cancer-induced indications, for example megestrol acetate to treat anorexia) may also be allowed at the discretion of the investigator.

Exemptions will be permitted on a case-by-case basis after prior approval by the Lilly clinical research physician (CRP)/clinical pharmacologist (CP) or designee if the investigator believes the patient's risk of recurrence and death is very low. Curatively treated nonmelanoma skin cancer or in situ carcinoma of any origin is allowed.

[8] Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

[9] If male or female with reproductive potential, agree to use medically approved contraceptive precautions during the trial and for 3 months following the last dose of study drug. In addition, male patients must not donate sperm during the trial and for 3 months following the last dose of study drug.

[10] If female with child bearing potential, must have a negative serum pregnancy test within 3 days of the first dose of study drug.

[11] Have an estimated life expectancy, in the judgment of the investigator, that will permit the patient to complete the drug interaction phase and at least 1 cycle of abemaciclib (if the patient were to participate in the safety extension).

[12] Are able to swallow capsules or tablets.

6.1.2. Exclusion Criteria

Potential study patients may not be included in the study if any of the following apply during screening.

[13] Have received treatment within 28 days of the initial dose of study drug with an investigational product (non-cancer-related therapies) or non-approved use of a drug or device (other than the study drug used in this study) or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[14] Have a personal history of any of the following conditions: presyncope or syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.

[15] Have known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated (eg, radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.

[16] Have a primary liver tumor.

[17] Have a clinically significant abnormal electrocardiogram (ECG) with any (but not limited to) the following findings: persistent and significant ventricular arrhythmia, evidence of acute myocardial ischemia, or QTc prolongation (defined as QT interval corrected for heart rate using Bazett's formula >470 msec).

[18] Have preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study (for example, history of major surgical resection involving the stomach or small bowel, nausea, vomiting, diarrhea, or malabsorption syndromes).

[19] Have lymphoma or leukemia.

[20] Have any history of receiving an autologous or allogeneic stem-cell or bone marrow transplant

[21] **For Periods 1 and 2:**

- Require treatment with inducers or inhibitors of CYP1A2, CYP2C9, CYP2D6, and CYP3A within 14 days before the first dose of study drug through the end of Period 2
- Require treatment with substrate drugs of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A with narrow therapeutic indices, at the discretion of the investigator following discussion and agreement with the Lilly CRP/CP or designee.

Note: Following Period 2 and during the remainder of the study:

Inducers and inhibitors of CYP3A, as well substrate drugs of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A with narrow therapeutic indices should be avoided (see Section 7.5 Concomitant Therapy).

[22] Require continued treatment with other drugs that are contraindicated with caffeine, warfarin, dextromethorphan, or midazolam.

[23] Have a known hypersensitivity to caffeine, warfarin, dextromethorphan, or midazolam.

[24] Are pregnant or lactating females.

[25] Have active bacterial, fungal, and/or known significant viral infection (for example, human immunodeficiency virus antibodies, hepatitis B surface antigen, or hepatitis C antibodies). Screening of these infections are not required for enrollment.

[26] History or presence of significant bleeding disorders that is, hematemesis, melanena, other known gastrointestinal bleeding (within the last 3-6 months) with significant risk of recurrence, severe or recurrent epistaxis, hemoptysis, clinically overt hematuria, or intracranial hemorrhage.

[27] Have a history of major head trauma (with loss of consciousness) within the past year or minor head trauma (without loss of consciousness) within the last 3 months prior to screening.

6.2. Summary of Study Design

This will be an open-label, 4-period, fixed-sequence study, followed by a safety extension phase, in patients with advanced and/or metastatic cancer.

The drug cocktail of 100 mg caffeine, 10 mg warfarin, 30 mg dextromethorphan, and 0.2 mg midazolam will be administered orally as a single dose on 2 occasions: Day 1 in Period 1, and in combination with abemaciclib on Day 8 of Period 2, after 7 days of 200 mg abemaciclib Q12H dosing. After completing Period 2, patients will continue to receive abemaciclib at a dose of 200 mg Q12H (or a modified dose) through the end of Periods 3 and 4, in 28-day cycles, and then may continue in a safety extension phase until discontinuation criteria are met. Patients who do not complete dosing and PK sampling through Period 2 may be replaced.

Patients will be provided with an electronic diary from the baseline visit through the end of Cycle 2 to record the time and date of abemaciclib administration, anti-diarrhea medications taken, and bowel habits and any changes.

The study design is illustrated in Figure JPCB.6.1.

Period 1

Patients will report to the study site within 7 days prior to the first dose of drug cocktail dosing for baseline safety assessments, initial diary training, and bowel habit assessment, and PRO scale completion. Patients will also be fitted with an ambulatory blood pressure monitor (ABPM) device for a 12-hour acclimation period between Days -7 to -2. Patients will begin collecting daily baseline diary assessments for bowel habits following the baseline visit. Patients will report to the study site on Day -2 or Day -1 prior to procedures and dosing on Day 1 for 24-hour ABPM measurements, which will serve as the baseline. Patients will then report to the study site prior to dosing on Day 1. On Day 1, patients will receive the drug cocktail, with single oral doses of 100 mg caffeine, 10 mg warfarin, 30 mg dextromethorphan, and 0.2 mg midazolam coadministered at the same time. Serial blood samples will be collected to determine the concentrations of caffeine, S-warfarin, dextromethorphan, and midazolam. Patients will be present at the study site for at least 12 hours after dosing, and then return to the study site on an outpatient basis for the collection of PK and/or PD samples.

Period 2

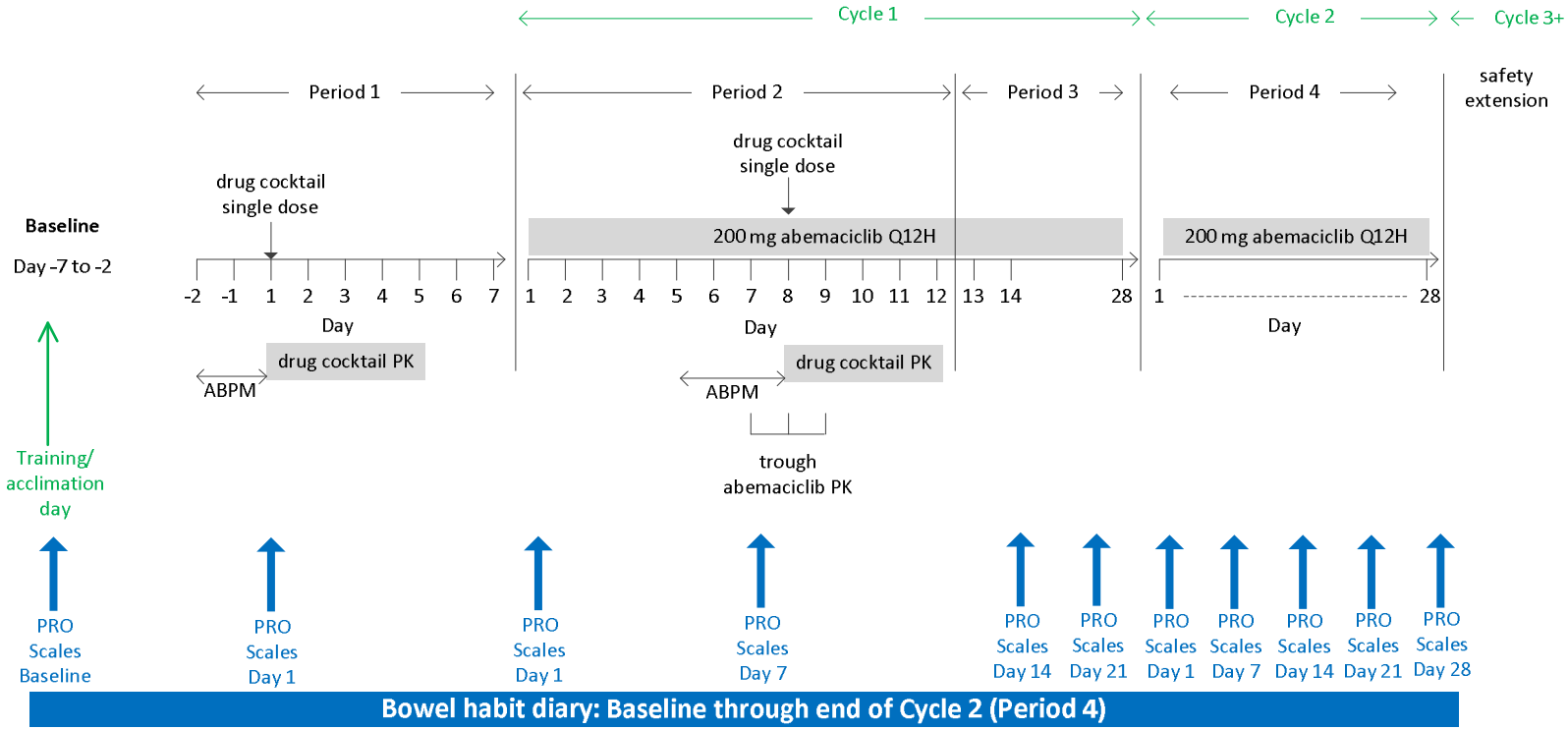
Period 2 will begin no earlier than 7 days after the cocktail dose in Period 1. Prior to abemaciclib dosing, safety assessments will be collected. Patients will receive the first dose of 200 mg abemaciclib at the study site and then will be released with a sufficient supply of abemaciclib for 8 days taken Q12H. Patients will report to the study site between Days 5 to 7 and will be fitted with an ABPM device for a 24-hour measurement after multiple doses of abemaciclib. Patients will report to the study site on Day 8 and will be coadministered abemaciclib and the drug cocktail in the morning. Serial blood samples will be collected after dosing on Day 8 to determine the concentrations of caffeine, S-warfarin, dextromethorphan, and midazolam. Blood samples will also be collected for the measurement of trough concentrations of abemaciclib. Patients will be present at the study site for at least 12 hours after dosing with the drug cocktail, and then released with a sufficient supply of abemaciclib. Patients will return to the study site on an outpatient basis for the collection of PK and/or PD samples.

Period 3 and 4

After completing Period 2, it is anticipated that patients will continue 200 mg abemaciclib Q12H during Periods 3 and 4 for assessment of bowel changes. This will complete Cycles 1 and 2 of abemaciclib treatment, as depicted in Figure JPCB.6.1.

Safety monitoring will be conducted throughout the entire study duration.

Refer to Attachment 1 for the Study Schedule.



Abbreviations: ABPM = ambulatory blood pressure monitoring; PK = pharmacokinetics; PRO = patient reported outcomes; Q12H = every 12 hours.

ABPM will be performed at following times: 12-hour acclimation period between Days -7 to -2 in Period 1, 24-hour period between Day -2 and dosing on Day 1 in Period 1, and 24-hour period between Days 5 to 8 in Period 2.

Figure JPCB.6.1. Study design.

6.2.1. Safety Extension Phase

Patients who participate in the safety extension phase of the study will receive an abemaciclib dose of 200 mg Q12H (or modified dose as applicable) on a 28-day cycle until discontinuation criteria are met (eg, disease progression, death, or unacceptable toxicity (Section 6.3). If interruptions in dosing are required for significant periods of time (> 14 days) continuation of treatment with abemaciclib may be considered if felt to be in the best interest of the patient's care and upon discussion with the medical monitor. Tumor re-staging may be allowed and will be documented when necessary.

Investigators may perform other standard procedures and tests needed to treat and evaluate patients; however, Lilly will not routinely collect the results of these assessments. Any AEs discovered during the safety extension phase will be collected.

The patient's participation in the safety extension period will be completed after therapy is discontinued. A follow-up assessment should occur approximately 10 days after the last abemaciclib dose is given. If a patient is required to begin a new treatment or investigational product, the follow-up assessment may take place sooner following discontinuation of study treatment.

While efficacy is not a primary objective of Study JPCB, responses will be followed and recorded by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria for solid tumors. Response data will be collected and tabulated.

6.2.2. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) after all patients have completed treatment and their safety summary visit. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed any applicable continued access follow-up.

6.2.3. Determination of Sample Size

Up to 48 patients may be enrolled in order that 22 patients complete Periods 1 and 2.

Caffeine

For caffeine area under the concentration time curve (AUC), the intra-subject variability (coefficient of variation) was estimated to be 21.0% (Blanchard and Sawers 1983); 22 patients will provide a precision of 0.13 on the log scale with 90% power.

Warfarin

For warfarin AUC, the intra-subject variability (coefficient of variation) was estimated to be 7% (Steinijans et al. 1995); 22 patients will provide a precision of 0.04, with 90% power, which corresponds to 4.4% on the log scale. For warfarin C_{max}, the intra-subject variability was

estimated to be 8% (Steinijans et al. 1995); 22 patients will provide a precision of 5.0% on the log scale with 90% power.

Dextromethorphan

For dextromethorphan AUC, the intra-subject variability (coefficient of variation) was estimated to be 33.7% (derived from a previous study); 22 patients will provide a precision of 0.20, with 90% power, which corresponds to 22.4% on the log scale. For dextromethorphan C_{max}, the intra-subject variability was estimated to be 32.1% (derived from a previous study); 22 patients will provide a precision of 21.3% on the log scale with 90% power.

Midazolam

For midazolam AUC, the intra-subject variability (coefficient of variation) was estimated to be 16.1% (derived from a previous study); 22 patients will provide a precision of 0.10, with 90% power, which corresponds to 10.4% on the log scale. For midazolam C_{max}, the intra-subject variability was estimated to be 26.4% (derived from a previous study); 22 patients will provide a precision of 17.3% on the log scale with 90% power.

ABPM

Using an intra-subject standard error of 9.48 mmHg in systolic blood pressure from Study JPBA, a sample size of 22 completed patients will provide more than 90% coverage probability that the half-width of the 90% confidence interval (CI) for the difference in means will be approximately 6 mmHg. The intra-subject standard error of diastolic blood pressure was estimated to be 6.78 mmHg and will provide more than 90% coverage probability that the half-width of the 90% CI is in difference of means to be 4.3 mmHg.

6.3. Discontinuations

The reason for and date of discontinuation will be collected for all patients. The date of discontinuation (for any of the above reasons) from study treatment is to be reported on the electronic case report form (eCRF). Patients who discontinue will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

If a patient withdraws informed consent, he or she must not be contacted unless he or she has explicitly provided permission and consent. Lilly may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization.

6.3.1. Discontinuation of Patients Inadvertently Enrolled

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor CRP and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the Lilly CRP agrees with the investigator that it is

medically appropriate for that patient. The patient may not continue in the study with or without investigational product if the Lilly CRP does not agree with the investigator's determination that it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

6.3.2. Discontinuation of Patients from Study or Study Drug

Patients who are discontinued from the study drug early will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

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

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator/Physician Decision
    - the investigator/physician decides that the patient should be discontinued from the study or study drug(s).
    - the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug(s) occurs prior to introduction of the other agent.
- Patient Decision
    - the patient requests to be discontinued from the study or study drug.
- Sponsor Decision
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.
- The patient has evidence of progressive disease.
- The patient experiences unacceptable toxicity.
- The patient is noncompliant with study procedures and/or treatment (Section 7.6).

6.3.3. Patients Lost to Follow-Up

A patient would 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.

6.3.4. Discontinuation of Study Sites

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

6.3.5. Discontinuation of the Study

The study will be discontinued if Lilly, while considering the rights, safety, and well-being of the patient(s), judges discontinuation of the study necessary for any scientific, medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7. Treatment

7.1. Materials and Supplies

Abemaciclib

Abemaciclib will be supplied as 50-mg capsules as the 25% w/w formulation (C3) for oral administration. The capsules should be stored at room temperature according to the range provided on the product label and not opened, crushed, or dissolved.

Drug Cocktail

The drug cocktail containing caffeine, warfarin, dextromethorphan, and midazolam will be sourced by the study sites.

Caffeine

Commercially available caffeine citrate solution (20 mg/mL) for oral administration.

Warfarin

Commercially available warfarin (brand name Coumadin) as 5-mg tablets for oral administration.

Dextromethorphan

Commercially available dextromethorphan as 15-mg liquid gel capsules for oral administration.

Midazolam

Commercially available midazolam syrup (2 mg/mL) for oral administration.

All clinical study materials will be labeled according to the country's regulatory requirements and stored according to the manufacturer's instructions.

7.2. Study Drug Administration

The investigator or designee is responsible for:

- explaining the correct use of the investigational agent(s) to the site personnel or patient,
- verifying that instructions are followed properly,
- maintaining accurate records of study drug dispensation, and collection, and returning or destroying all unused medication to Lilly or its designee at the end of the study.

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

The first dose of abemaciclib will be given to the patient at the site. The date and time of the dose should be documented in the research records. While patients are outside the study site, they will be asked to self-administer doses of abemaciclib. The actual time of all abemaciclib

dose administrations will be recorded in the patients' diary during Period 1, Period 2, Period 3, and Period 4.

7.2.1. Dosing Schedule

Period 1

On Day 1, 10 mL of 20-mg/mL caffeine citrate solution (100 mg caffeine), 2 × 5-mg tablets of warfarin, 2 × 15-mg liquid gel capsules of dextromethorphan, and 0.1 mL of 2-mg/mL midazolam syrup will be coadministered orally with approximately 240 mL of room temperature water, in a sitting position.

Patients should not consume food beginning 1 hour before and ending 1 hour after taking study drugs.

Period 2

On Days 1 to 12, 4 × 50-mg capsules of abemaciclib will be administered orally in the morning and evening with approximately 240 mL of room temperature water, in a sitting position. Abemaciclib should be taken at approximately the same time each day. On Day 8, abemaciclib will be coadministered with 10 mL of 20-mg/mL caffeine citrate solution (100 mg caffeine), 2 × 5-mg tablets of warfarin, 2 × 15-mg liquid gel capsules of dextromethorphan, and 0.1 mL of 2-mg/mL midazolam syrup with approximately 240 mL of room temperature water, in a sitting position. On Day 8 (coadministration with the drug cocktail), patients should not consume food beginning 1 hour before and ending 1 hour after taking study drugs.

If a patient has an INR >2 after the first dose of warfarin, the patient may receive the drug cocktail without warfarin in Period 2 and receive abemaciclib once their INR has stabilized or returned to baseline.

If a patient misses or vomits a dose of abemaciclib, that dose should be omitted (see Section 7.6 for compliance). Patients will be asked to take each dose of study drug within +/- 2 hours of the planned dose time or consider the dose a missed dose.

Periods 3, 4 and Safety Extension Phase

From Cycle 1, Period 3 and on Days 1 to 28 in each cycle (Cycle 2 onwards), 4 × 50-mg capsule of abemaciclib will be taken orally in the morning and evening. Abemaciclib should be taken at approximately the same time each day.

A delay of ≤7 days in the start of a cycle (Day 1) for justifiable reasons (for example, inclement weather, holidays, or weekends) other than toxicity will be permitted and does not constitute a protocol violation. A delay of ≤14 days in the start of a cycle (Day 1) to allow for recovery from toxicity will be permitted and does not constitute a protocol violation. A longer delay may be allowed for the start of Cycle 1 (or Period 2), if necessary. In cases where Cycle 1 (abemaciclib dosing) is significantly delayed from tumor staging during screening, baseline staging may be repeated. If there is any question, this may be discussed with the study medical monitor.

If a patient requires omission of >25% of doses for tolerability at the reduced dose level, then treatment may continue if the investigator determines that the patient is receiving clinical benefit.

For patients requiring dose reduction(s) due to toxicity, reescalation to a prior dose level is not permitted without prior discussion and agreement with the Lilly CRP/CP or designee.

7.2.2. Dose Adjustments

Period 2

Dose interruptions or adjustments should be avoided in Period 2 but are allowed if necessary due to toxicity.

Upon the first sign of diarrhea, patients should be treated with loperamide and supportive care before the abemaciclib dose is omitted or adjusted (see Section 8.1.3.4.1). If diarrhea is Grade 2 or worse and does not resolve within 1 day with loperamide and supportive care treatment, then the dose should be suspended (until the toxicity resolves to at least Grade 1) and the dose of study drug may be reduced to 150 mg Q12H. Further dose modification due to diarrhea should be discussed with the Lilly CRP/CP or designee, and continuation in study determined jointly as described in Section 7.6.

If it is deemed the patient must be replaced due to dosing omissions or dose reductions, the patient may continue on study to receive abemaciclib and complete all other study procedures for secondary and exploratory study objectives.

Periods 3, 4, and Safety Extension

Dose adjustments are allowed during Period 3, Period 4, and the safety extension phase, both within a cycle and between cycles following Table JPCB.7.1. Study drug dose reductions are outlined in Table JPCB.7.2.

Before the start of each cycle, drug-related toxicities (except alopecia and fatigue) must resolve to either baseline or at least Grade 2. The start of a cycle may be delayed up to 14 days to allow sufficient time for recovery. Patients not recovering from toxicity within 14 days should be discontinued from the study.

Table JPCB.7.1. Toxicity Dose Adjustments and Delays of Abemaciclib for Study JPCB

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Neutropenia/thrombocytopenia Section 7.2.2.1	Grade 3 which lasts 7 days	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Neutropenia/thrombocytopenia Section 7.2.2.1	Recurrent Grade 3 (on later cycle) which lasts 7 days	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Neutropenia/thrombocytopenia Section 7.2.2.1	Grade 4 which lasts 3 days	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic toxicity: **Patient requires administration of white blood cell growth factors** Section 7.2.2.1	Regardless of severity (Growth factors use according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of white 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 lead to the use of white blood cell growth factor.
Nonhematologic Toxicity (except diarrhea) Section 7.2.2.2.1	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MAY** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Nonhematologic Toxicity Section 7.2.2.2.1	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Section 7.2.2.2.2	Requires hospitalization or Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Section 7.2.2.2.2	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 24 hours to at least Grade 1	Dose **SHOULD** be suspended until toxicity resolves to at least Grade 1.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Diarrhea Section 7.2.2.2.2	Diarrhea recurs despite maximal supportive measures after resuming same dose level after initial Grade 2 diarrhea	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.

Abbreviation: ASCO = American Society of Clinical Oncology.

Note: MAY = per the investigator's clinical judgment; SHOULD = not mandatory but highly recommended; MUST = mandatory.

Table JPCB.7.2. Dose Adjustments for Abemaciclib during Period 3, Period 4, and Safety Extension

Dose adjustment	Oral dose	Frequency
0	200 mg	Q12H
1	150 mg	Q12H
2	100 mg	Q12H
3	50 mg	Q 12H

7.2.2.1. Hematologic Toxicity

If a patient experiences Grade 4 neutropenia/thrombocytopenia, which lasts 3 days, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of abemaciclib must be reduced as outlined in Table JPCB.7.2.

If a patient experiences Grade 3 neutropenia/thrombocytopenia, which lasts 7 days, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of abemaciclib may be reduced by 1 dose level. If the patient experiences a recurrent episode of Grade 3 neutropenia/thrombocytopenia in a later cycle, which lasts 7 days, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of abemaciclib may be reduced by 1 dose level.

If a patient requires administration of white blood cell growth factors, the dose of study drug must be suspended for at least 48 hours after the last dose of white blood cell growth factors was administered and until toxicity resolves to at least Grade 2, then reduced by 1 dose level, if a dose reduction for the specific event necessitating the use of the white blood cell growth factors has not already occurred.

Before the start of each cycle, hematologic toxicity possibly related to abemaciclib must resolve to at least Grade 2.

7.2.2.2. Nonhematologic Toxicity

7.2.2.2.1. Dose Adjustments for Other Nonhematologic Toxicity

If a patient experiences ≥ Grade 3 nonhematologic toxicity possibly related to abemaciclib, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib must be reduced as outlined in Table JPCB.7.2.

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea; refer to Section 7.2.2.2.2) possibly related to abemaciclib that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, then dosing may be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib may be reduced as outlined in Table JPCB.7.2.

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

7.2.2.2.2. Diarrhea

A patient experiencing diarrhea requiring hospitalization (irrespective of grade, that is, requiring intravenous [IV] rehydration) or severe diarrhea (Grade 3 or 4) must have study treatment suspended (until the toxicity resolves to at least Grade 1) and should have the study drug dose reduced by 1 dose level as outlined in Table JPCB.7.2.

If a patient experiences persistent or recurrent diarrhea that does not resolve with maximal supportive measures (refer to Section 8.1.3.4.1) within 24 hours to at least Grade 1, then study treatment should be suspended (until the toxicity resolves to at least Grade 1) and the dose of study drug may be reduced by 1 dose level as outlined in Table JPCB.7.2 at the discretion of the investigator. If the same dose level was resumed and diarrhea recurs despite maximal supportive measures, the dose of study drug must be reduced by 1 dose level as outlined in Table JPCB.7.2.

7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive the fixed-sequence of treatments in this study.

7.4. Blinding

This is an open-label study.

7.5. Concomitant Therapy

No other chemotherapy, radiotherapy, immunotherapy, cancer-related hormone therapy, or experimental drugs will be permitted while the patients are on this study, except for those described in Inclusion Criterion [7] in Section 6.1.1.

The need for radiotherapy will be cause for early discontinuation from the study, with the exception of palliative radiotherapy, which is permitted if not being utilized for disease progression. In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study.

Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the case report form (CRF). Patients will be provided with a paper diary in which to record the start and stop times of new concomitant medications and medications taken as needed from the baseline visit until the end of Period 2.

7.5.1. Interactions of Concomitant Medications with Abemaciclib

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

7.5.1.1. CYP Interactions

Agents considered to be CYP3A inhibitors and CYP3A inducers are excluded from use 14 days before the first dose of study drug and through the end of Period 2. It is recommended that CYP3A inducers and CYP3A inhibitors, as well substrate drugs of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A with narrow therapeutic indices be avoided.

7.5.1.2. Endocrine Therapy

Since functional loss of Rb activity is associated with resistance to hormonal therapy in breast and prostate cancers (reviewed in Knudsen and Knudsen 2008), patients with prostate cancer progressing on endocrine therapies may in certain cases have that treatment continued while receiving study drug. Patients with breast cancer who are receiving aromatase inhibitors (letrozole, anastrozole, or exemestane) or antiestrogens (fulvestrant or tamoxifen) may not participate, as the abemaciclib starting dose for this subset of patients is 150mg Q12H. Patients with prostate cancer may continue to receive luteinizing-hormone-releasing hormone analogue therapy (leuprolide, goserelin, or triptorelin) during the study. In addition, hormone replacement therapy initiated before study entry may be continued.

7.5.1.3. Growth Factors

Patients should receive full supportive care during the trial. Growth factors should not be administered to enable a patient to satisfy study inclusion criteria. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2015) if clinically indicated. Dosing of study drug must be suspended if the administration of white blood cell 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 white blood cell growth factors, the dose of study drug must be reduced by one dose level, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred. Before the start of each cycle, hematologic toxicity must resolve to either baseline or at least Grade 2.

Erythroid-stimulating agents (ESAs, including erythropoietin and darbepoetin) or transfusions should not be administered to enable a patient to satisfy study inclusion criteria. Both ESAs and transfusion therapy may be used in accordance with American Society of Hematology and ASCO guidelines (Rizzo et al. 2010), if clinically indicated.

7.5.2. Interactions of Concomitant Medications with Drug Cocktail

Caffeine, warfarin, dextromethorphan, and midazolam are substrates of CYP1A2, CYP2C9, CYP2D6, and CYP3A, respectively. Thus, drugs that are known inducers and/or inhibitors of CYP1A2, CYP2C9, CYP2D6, and CYP3A are specifically excluded prior to 14 days of drug cocktail administration and throughout Periods 1 and 2. Since caffeine is one of the substrate drugs being evaluated in this study, consumption of caffeine-containing beverages and foods must be avoided at least 5 days prior to drug cocktail administration and throughout Periods 1 and 2. Subjects must also refrain from consuming grape fruit juice, Seville oranges, and St. John's wort 14 days prior to the cocktail administration and throughout Periods 1 and 2.

The investigator should refer to the prescribing label for each drug within the cocktail for additional information about the potential for drug interactions.

For information about contraindications of other drugs indicated in combination with the drug cocktail, investigators should refer to the contraindications section of the package inserts.

7.6. Treatment Compliance

The drug cocktail will be administered orally twice at the study site, under the direction of the investigator in Periods 1 and 2. As a result, a patient's compliance with drug cocktail administration is ensured for these periods.

Patients are expected to be compliant with all doses of study medication. Patients should attend scheduled clinic visits and must comply with study criteria under their control. Deviation(s) from the prescribed dosage regimen should be recorded on the CRF.

Patient compliance with abemaciclib will be assessed when patients return to the clinic during Periods 2, 3, and 4. Compliance will be assessed through review of patient diary, direct questioning, and counting of returned tablets. Deviation(s) from the prescribed dosage regimen should be recorded on the CRF.

If a patient misses 2 or more of the planned doses of abemaciclib within 3 consecutive days prior to the drug cocktail dose in Period 2, the patient will need to be replaced, or dosing with the drug cocktail may be delayed to allow for adequate exposure. Delay should only occur on a case-by-case basis following discussion and agreement with the Lilly CRP/CP or designee. Likewise, if dose reduction is required to less than 150mg Q12H or if dose interruptions or omissions are deemed necessary during Period 2 for greater than 4 consecutive doses at any time, the patient may recommence dosing of abemaciclib with delay of Period 2 drug cocktail dosing so that abemaciclib steady state is achieved (5-7 days).

During the safety extension phase, patient compliance with abemaciclib will be assessed and recorded at each visit by counting returned capsules.

Similarly, a patient may be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication. Any missed doses will be omitted and not replaced. In the event of a missed dose, a patient should resume and continue dosing beginning with the next scheduled dose. Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP/CP or designee before making the final determination for discontinuation. If a patient is discontinued because of study drug noncompliance, the patient may be replaced.

The following procedures will be employed to ensure appropriate drug accountability:

- Drug accountability will be emphasized at the study initiation.
- Drug accountability will be monitored throughout the study.
- Each patient should be instructed to return all study drug packaging and unused material to the study site at each visit. The study site will keep a record of all study drug dispensed to and returned by the patients throughout the study. Study site personnel will return or destroy (as requested) all unused study drug for all patients.

7.6.1. Evaluable Patients

Patients who withdraw from the study before receiving study drug(s) will be replaced and will not be included in the safety or efficacy assessments. Safety analyses will be conducted on all patients who have received at least 1 dose of study drug.

Any patient who does not complete the drug interaction portion of the study (Periods 1 and 2, including all of the PK sampling) at a dose of either 200 mg Q12H or 150 mg Q12H will be deemed nonevaluable for the drug interaction analyses and should be replaced after consultation with the investigator(s) and the Lilly CRP/CP or designee to ensure adequate PK data to evaluate the drug interaction. Patients who are deemed nonevaluable for drug interaction analyses may continue on study, receive abemaciclib, and complete all other study procedures for secondary and exploratory study objectives.

8. Safety, Pharmacokinetic, Pharmacodynamic, and Efficacy Data Collection

8.1. Safety Evaluations

The safety and tolerability of abemaciclib have been assessed in nonclinical toxicology studies and the results from these studies are detailed in the IB. This Phase 1 study contains detailed safety monitoring that will permit initial characterization of the safety profile of abemaciclib in patients. Study procedures and their timing, including collection of blood and urine samples, are described in the Study Schedule (Attachment 1).

Standard laboratory tests, including chemistry, hematology, and urinalysis panels, will be performed. A pregnancy test will be administered if applicable. Other clinical laboratory tests will also be collected. Attachment 2 lists the specific tests that will be performed for this study. Vital signs, ABPM, and ECGs will also be performed.

8.1.1. Safety Data Collection and Review

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JPCB.8.1 presents a summary of AE and SAE reporting guidelines.

8.1.2. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which 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 medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any clinically significant findings from labs, vital sign measurements, and so on that occur should also be reported to Lilly or its designee as an AE. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

The investigator, monitor, and sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the Study Schedule. Patients will be provided with a paper diary in which to record the start and stop times of all AEs experienced from the baseline visit until the end of Period 2.

The Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. All AEs observed will be graded using CTCAE v 4.0. Any minor version of CTCAE v 4.0 (for example, Version 4.03) may be used for this study. Minor CTCAE v 4.0 updates from the NCI will not necessitate a protocol amendment. For AEs without matching terminology within the CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the CRF. This collection is in addition to verbatim text used to describe the AE.

In addition to collecting the AE verbatim, the CTCAE term, and the CTCAE severity grade, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities dictionary.

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breastfeeding should be collected, if feasible, for regulatory reporting and drug safety evaluation.

Upon documentation of pregnancy, the patient must be removed from the study and treatment with study drug(s) must be stopped immediately.

For all enrolled patients, study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. While the patient is on study, site personnel will record any change in these preexisting condition(s) and the occurrence and nature of any AEs. In addition all AEs related to protocol procedures are reported to Lilly or designee.

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

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

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

- **Related**: a direct cause and effect relationship between the study treatment and the AE is likely.

- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Unrelated**: without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures, all "related" and "possibly related" AEs and SAEs will be defined as related to study drug.

8.1.2.1. Serious Adverse Events

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

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

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

- death
- initial or prolonged inpatient hospitalization (except for study drug administration)
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

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

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

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

8.1.2.2. Adverse Event and Serious Adverse Event Reporting

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

8.1.2.2.1. Prior to Administration of Study Drug(s)

During screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected after the patient has signed the informed consent form (ICF). For patients who do not enroll in the trial (that is, have not received at least 1 dose of abemaciclib), only AEs and SAEs related to protocol procedures are required to be collected.

8.1.2.2.2. On Study Treatment

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring while the patient is receiving study drug must be reported to Lilly or its designee. A patient is considered to be receiving study drug from the time he/she receives the first dose of study drug to when he/she receives the last dose of study drug.

8.1.2.2.3. Follow-Up Visit

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring during the follow-up visit must be reported to Lilly or its designee. For patients not continuing in the safety extension phase, the follow-up visit should occur after a washout period of at least 10 days from the last abemaciclib dose in Period 2. For patients participating in the safety extension phase, a follow-up visit should occur approximately 10 days after the last abemaciclib dose. At this follow-up visit, the patient will be required to have specific safety assessments (Attachment 1). The timing of these safety assessments are outlined in Attachment 1.

Following the safety assessments, which mark the end of the follow-up visit, the patient will be discontinued from the study, unless there is an ongoing AE or SAE that is possibly related to study drug. In this instance, the patient should be followed in subsequent follow-up visits until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up.

If it is deemed to be in the best interest of the patient to start a new anticancer treatment prior to the scheduled end of the follow-up visit, the follow-up visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

After the follow-up visit, AEs are not required to be reported unless the investigator feels the AEs were related to either study drug or a protocol procedure. If an investigator becomes aware of SAEs believed to be related to protocol procedures or study drug, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

8.1.2.3. Suspected Unexpected Serious Adverse Reactions

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

8.1.2.4. Summary of Adverse Event/Serious Adverse Event Reporting Guidelines

The AE and SAE reporting guidelines are summarized in Table JPCB.8.1.

Table JPCB.8.1. Adverse Event and Serious Adverse Reporting Guidelines for Study JPCB

Timing	Types of AEs/SAEs Reported
Prestudy (baseline assessments) (Starts at the signing of informed consent and ends just before the first dose of study drug)	Preexisting conditions All AEs/SAEs possibly related to protocol procedures
On therapy (Starts at first dose of study drug(s) and ends at last dose of study drug[s])	All AEs/SAEs regardless of relatedness
Follow-up visit End of Period 2: starts after the last PK sample and ends when end of study safety assessments are completed Safety extension: starts just after the last dose of study drugs and ends when end of study safety assessments are completed	All AEs/SAEs regardless of relatedness
Subsequent follow-up visits, if necessary	Ongoing or new AEs/SAEs possibly related to study drug or protocol procedures

Abbreviations: AE = adverse event; PK = pharmacokinetic; SAE = serious adverse event.

8.1.3. Other Safety Measures

8.1.3.1. Vital Signs

Blood pressure, pulse rate, and body temperature will be measured as specified in the Study Schedule and as clinically indicated (Attachment 1).

Blood pressure and pulse rate should be measured after at least 5 minutes supine, semi-recumbent, or sitting; the position should be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted and agreed upon between the sponsor and investigator.

8.1.3.2. Ambulatory Blood Pressure Monitoring

Blood pressure and pulse rate will be measured using an ABPM device over a 12-hour period for acclimation and over 24-hour periods for study assessments as specified in the Study Schedule (Attachment 1).

The ABPM device will be fitted to the patient's nondominant arm and will record ambulatory blood pressure and pulse rate every 30 minutes during the day (for example, 0700 hours to 2200 hours) and every 2 hours at night (for example, 2200 hours to 0700 hours). For each 24-hour ABPM collection period, patients will be encouraged to maintain light activity (that is, walking) and keep their same routine during the ABPM collection period. ABPM data will not be used for patient management.

8.1.3.3. Electrocardiograms

For each patient, a 12-lead digital ECG will be collected according to the Study Schedule (Attachment 1). Patients must be supine or semi-recumbent for approximately 5 to 10 minutes before ECG collection and remain supine or semi-recumbent but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed to ensure high quality records.

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

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

8.1.3.4. Bowel Habits

8.1.3.4.1. Diarrhea Management

In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

- Upon enrollment, patients should receive instructions in the event that a patient would experience diarrhea
- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (e.g. loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 1 day.

- If diarrhea does not resolve with anti-diarrheal therapy within 1 day to either baseline or Grade 1, abemaciclib should be suspended or the dose may be reduced until diarrhea is resolved to baseline or Grade 1 (see Section 7.2.2).
- When abemaciclib recommences, dosing should be adjusted as outlined in Table JPCB.7.1.

In severe cases of diarrhea, measuring neutrophil counts and body temperature and proactively managing diarrhea with anti-diarrheal agents should be considered.

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

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

Osmolality will be measured to assist with evaluation of any change in volume. In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with anti-diarrheal agents should be considered.

8.1.3.4.2. Patient Diary

An electronic patient diary to collect date and time of bowel movements, a Bristol Stool Chart, and drug administration will be completed daily by the patient, starting at baseline and required through end of Period 2. Patients participating in Period 3 and 4 should continue completing diary entries through end of Period 4. Patients will also receive a paper diary in which to record the start and stop times of all AEs, new concomitant medications and medications taken as needed from the baseline visit until the end of Period 2.

8.1.3.4.3. Patient Reported Outcomes

Collection of PRO data will help characterize diarrhea as an exploratory analysis based on:

- Single daily items generated by the team
- Weekly items based on the FACIT-D

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

At each time point identified in the Study Schedule (Attachment 1), a copy of the PRO items should be completed by the patient prior to extensive interaction with site staff and study drug administration.

8.1.4. Safety Monitoring

The Lilly CRP/Clinical Research Scientist (CRS) will monitor safety data throughout the course of the study.

Representatives from Lilly Global Patient Safety will specifically monitor SAEs. Lilly will review SAEs within time frames mandated by company standard operating procedures. The Lilly CRP/CRS will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist, and periodically review:

- trends in safety data,
- laboratory analytes,
- AEs,
- if a study patient experiences elevated ALT ≥5X ULN and elevated total bilirubin ≥2X ULN, clinical and laboratory monitoring should be initiated by the investigator.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CP or designee regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3).

8.1.5. Complaint Handling

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

Complaints related to comparator drugs or concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

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

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

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

8.2. Sample Collection and Testing

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

Attachment 2 lists the specific tests that will be performed for this study.

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

8.2.1. Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results

are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.2.2. Samples for Drug Concentration and Pharmacodynamic Measurements

8.2.2.1. Pharmacokinetic Samples

At the visits and times specified in the Study Schedule (Attachment 1), venous blood samples will be collected to determine the plasma concentrations of abemaciclib, caffeine, S-warfarin, dextromethorphan, and midazolam. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and Lilly. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

These samples will be analyzed at a laboratory designated by the sponsor. Plasma concentrations of each analyte will be assayed using a validated method.

The PK samples will be stored at a facility designated by the sponsor.

The remaining plasma from the samples collected for PK may be pooled and used for exploratory metabolism work as deemed appropriate.

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

8.2.2.2. Pharmacodynamic Samples

At the visits and times specified in the Study Schedule (Attachment 1), venous blood samples will be collected to determine INR (see Attachment for the blood sampling summary). Analysis of PT or INR will be performed by local labs. Local labs for PT or INR will be collected for patient management and PD analyses.

Guidance Regarding Elevation of the INR

Patients will receive a single dose of warfarin (10 mg) as part of the drug cocktail in Period 1 and Period 2:

> Period 1: If a patient has an INR >2 after the first dose of warfarin, the patient should not receive warfarin again in the drug cocktail in Period 2, but may be allowed to enter Period 2 and receive abemaciclib once their INR has stabilized or returned to baseline. The patient may be replaced.
>
> Period 2: For any patient found to have an INR ≥4 after the administration of warfarin in Period 2, further abemaciclib dosing should be held until the INR stabilizes or returns to baseline (refer to Section 7.2.2).

Additionally the following guidance is provided (Cushman et al. 2014):

- If the INR is >4 but <9, and there is no significant bleeding, oral vitamin K (1 to 2.5 mg) is recommended.
- If the INR is ≥9, and there is no significant bleeding, oral vitamin K (2.5 to 5 mg) is recommended.
- In the case of significant bleeding, additional supportive care is recommended (for example, prothrombin complex concentrates and vitamin K 10 mg, by oral or slow intravenous infusion).

The INR should be repeated according to the Study Schedule (Attachment 1); additional INR samples may be collected daily, if needed, until the INR has returned to baseline. The final decision as to whether to administer vitamin K or other therapy should take into account the investigator's assessment of the patient.

Lilly should be notified in the case of the INR elevations as described above.

The samples will be identified by the patient number (coded) and stored for up a maximum of 1 year after the last patient visit for the study at a facility selected by the sponsor.

8.2.3. Samples for Evaluation of Renal Function

At the visits and times specified in the Study Schedule (Attachment 1), venous blood samples (approximately 5 mL each) will be collected to determine serum concentrations of renal markers, including creatinine, cystatin-C, and NGAL, and urine samples (at least 5 mL and up to 120 mL) will be collected to determine urinary concentrations of renal markers, including creatinine, KIM-1, and NGAL. These laboratory tests will be performed by a central laboratory selected by Lilly. Other markers of renal function may be evaluated if deemed appropriate.

The samples will be identified by patient number and will be stored for up to a maximum of 15 years after the last patient visit for the study.

8.2.4. Samples for Tailoring Biomarkers

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

Samples will be stored and analysis may be performed on biomarker variants thought to play a role in cancer, including, but not limited to, genes involved in regulation of the cell cycle to evaluate their association with observed clinical outcomes to abemaciclib.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to study drug. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and

drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

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

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

8.2.5. CYP Genotype Evaluation

A single blood sample will be collected from patients to determine the CYP2C9, CYP2D6, CYP3A4, and CYP3A5 genotype status during screening.

8.3. Efficacy Evaluations

Refer to Attachment 1 for details regarding the timing of specific efficacy measures.

Tumor assessments will be conducted per standard of care. Response and progression for tumors will be evaluated using RECIST version 1.1 (Eisenhauer et al. 2009).

8.3.1. Prestudy

No more than 4 weeks before enrolling in the study, each patient's full extent of disease will be assessed by 1 or more of the following relevant radiological tests for tumor measurement:

- computed tomography (CT) scan
- magnetic resonance imaging (MRI)
- chest x-ray
- bone scan

No more than 2 weeks (14 days) prior to enrolling in the study, each patient's full extent of disease will also be assessed with:

- tumor measurement of palpable or visible lesions (refer to RECIST 1.1)
- evaluation of tumor markers, if indicated

8.3.2. During the Study

At the intervals stated in the Study Schedule (Attachment 1), efficacy will be examined in each patient by the following evaluations:

- ECOG performance status (Attachment 5)
- tumor measurement of palpable or visible lesions
- imaging studies of involved disease sites should be repeated in appropriate patients per standard of care, approximately every 2 cycles (approximately 4 to 8 weeks). This should include the same methods and techniques used at baseline to ensure that any response may be validated.

All lesion assessments, whether by physical examination or radiological methods, must be repeated by the same method at least 4 weeks following the initial observation of an objective response for response confirmation.

8.3.3. Poststudy Follow-Up

The poststudy evaluation period will begin when the patient discontinues treatment from the safety extension period for any reason and will end approximately 10 days following the last abemaciclib dose, when another therapy is initiated, or when the patient dies. Reasonable efforts will be made to follow any patient with an ongoing complete response or partial response at the time of study discontinuation. In appropriate patients, tumor measurements and imaging studies will be performed at 4- to 8-week intervals up until 30 days after final abemaciclib dose, when another therapy is initiated, when there is disease progression, or when the patient dies. All patients will be evaluated for ECOG performance status (Attachment 5) at the poststudy follow-up visit.

8.4. Procedure/Sampling Compliance

Every attempt will be made to enroll patients who have the ability to understand and comply with instructions. Noncompliant patients may be discontinued from the study.

The collection times of safety assessments, PK samples, and efficacy measurements are given as targets, to be achieved within reasonable limits. The scheduled time points may be subject to minor alterations; however, the actual collection time must be correctly recorded on the eCRF.

The scheduled collection times may be modified by the sponsor based on analysis of the safety and PK information obtained during the study. Any major modifications that might affect the conduct of the study, patient safety, and/or data integrity will be detailed in a protocol amendment.

9. Data Management Methods

9.1. Data Quality Assurance

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

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

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

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

9.2. Data Capture Systems

9.2.1. Case Report Form

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

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome measures (for example, a rating scale), a daily dosing schedule or an event diary.

If information reported during an office visit differs from that recorded in the paper diaries, the source data (collected during patient interview) will supersede for purposes of collection in the CRF.

For data handled by a data management third-party organization (TPO), CRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the Lilly data warehouse, using standard Lilly file transfer processes.

For data handled by the sponsor internally, CRF data and some or all data that are related will be managed by the sponsor and stored electronically in the sponsor's system.

9.2.2. Ancillary Data

Data managed by a central vendor will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

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

Data from ePRO forms (if used) will be transferred from the ePRO vendor to the Lilly data warehouse.

10. Data Analyses

10.1. General Considerations

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

The interpretation of the study results will be the responsibility of the investigator with the Lilly CRP/CP or designee, pharmacokineticist, and statistician. The CRP/CP and statistician will also be responsible for the appropriate conduct of an internal review for both the final study report and any study-related material to be authorized by Lilly for publication.

Pharmacokinetic analyses will be conducted on data from patients who have received at least 1 dose of the study drug and have had samples collected.

10.2. Patient Disposition

All patient discontinuations will be documented, and the extent of each patient's participation in the study will be reported. If known, a reason for their discontinuation will be given.

10.3. Patient Characteristics

Patient characteristics will include a summary of the following:

- patient demographics including age, sex, screening height and weight, and screening body mass index will be reported
- baseline disease characteristics
- prior disease-related therapies
- concomitant medications.

Other patient characteristics will be summarized as deemed appropriate.

10.4. Safety Analyses

All patients who receive at least 1 dose of study drug will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE, Version 4.0).

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- dose adjustments
- clinical laboratory values including markers of renal function
- vital signs
- ABPM data
- ECGs
- bowel habit data
  - diarrhea diary and stool assessment
  - diarrhea-related ePRO items

An exploratory safety analysis will assess the impact of abemaciclib on markers of renal function, levels of creatinine, cystatin-C, KIM-1, and NGAL at predose (baseline) will be compared to postdose levels and results will be summarized using standard descriptive statistics.

Further analysis details will be described in the statistical analysis plan.

10.5. Pharmacokinetic Analyses

Pharmacokinetic parameter estimates for caffeine, S-warfarin, dextromethorphan, and midazolam will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max}, AUC from zero to infinity (AUC[0-∞]), and t_{max}. Other noncompartmental parameters, such as AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]), time of $t_{1/2}$, apparent clearance, and apparent volume of distribution may be reported. Additional exploratory analyses on the components of the drug cocktail or abemaciclib will be performed if warranted by data.

Pharmacokinetic parameter estimates will be evaluated to delineate effects of drug interaction. Caffeine, warfarin, dextromethorphan, and midazolam administered in the absence of abemaciclib will represent the reference treatments and be analyzed separately. Each drug administered with abemaciclib will represent the test treatments. Log-transformed C_{max} and AUC(0-∞) estimates will be evaluated in a linear mixed-effects analysis of variance model with a fixed effect for treatment and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CIs.

The t_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, 90% CIs, and p-values from the Wilcoxon test will be calculated.

The inter- and intra-subject variability will be reported for each probe drug.

Trough plasma concentrations of abemaciclib will be listed.

10.6. Pharmacodynamic Analyses

Area under the INR curve (AUC_{INR}) and maximum observed INR response (INR_{max}) will be calculated to quantify the action of warfarin.

The PD parameters AUC_{INR} and INR_{max} will be evaluated statistically to delineate the effect of abemaciclib on INR. A linear mixed-effects model with log-transformed PD parameter as a response variable, predose INR as a covariate, treatment as a fixed effect, and subject as a random effect. For each of these PD parameters, the statistical inference will be made using the test treatment of warfarin + abemaciclib and the reference treatment of warfarin in the absence of abemaciclib. The geometric means for the treatments and the ratios of geometric means for AUC_{INR} and INR_{max}, between the test and reference treatments with 90% CIs will be established.

10.7. Efficacy

The study was not designed to make an efficacy assessment. However, any tumor response data will be tabulated.

10.8. Interim Analyses

An interim analysis, which will serve as the final analysis for the primary objective, is planned for this study. This interim analysis will be completed after the last patient has completed Period 2.

Patients will be allowed to continue receiving abemaciclib during Period 3, 4, and the safety extension phase until discontinuation criteria are met (such as progressive disease or unacceptable toxicity). A final analysis and final study report will be completed after the last patient visit has occurred for this extension phase.

Two additional interim analyses may be conducted: one analysis will be conducted after approximately half of the patients have completed Periods 1 and 2, as a preliminary assessment of the magnitude of any observed effect on blood pressure. No changes to the study design are planned. Another analysis will be conducted after the last patient has completed Period 4 and a preliminary study report will be written.

Unplanned interims may be conducted if deemed necessary by Lilly study team.

This is an open-label study. Data may be analyzed while the trial is ongoing. An Assessment Committee will not be formed.

11. Informed Consent, Ethical Review, and Regulatory Considerations

11.1. Informed Consent

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

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

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

11.2. Ethical Review

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

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

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

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

11.3. Regulatory Considerations

This study will be conducted in accordance with:

1) 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

2) the ICH GCP Guideline [E6]

3) applicable laws and regulations.

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

Some of the obligations of the sponsor will be assigned to a TPO.

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

11.3.1. Investigator Information

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

11.3.2. Protocol Signatures

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

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

11.3.3. Final Report Signature

The final report coordinating investigator or designee will sign the clinical study report 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.

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

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Attachment 1. Protocol JPCB Study Schedule

Study I3Y-MC-JPCB Study Schedule for Screening, and Periods 1 and 2

	Screen		Period 1: Drug cocktail			Period 2 (Cycle 1, Days 1-12): Abemaciclib + drug cocktail				Early discharge/ follow up[a]
Study Day	**≤ -30**	**Baseline ≤ -7**	**-1**	**1**	**2-7**	**1**	**2-7**	**8**	**9-12**	
Informed consent	X[q]									
Medical history[m]	X									
Pregnancy test (if applicable)	X	X[b]								
Urinalysis	X	X[b]			X (Day 7)				X (Day 9)	X
Renal markers				Predose[l]				Predose 8 h[r]	24, 72 h (Days 9, 11)	
Hematology and serum chemistry	X	X[b]			X (Day 7)			Predose, 8h[j,r]	24, 72 h (Days 9, 11)	X
Physical exam & ECOG status	X	X[b,c]				Predose[c]			24 h (Day 9)[c]	X[c]
Weight	X	X				X				X
Vital signs[d]	X	X[b]		Predose, 2, 8 h	24 h (Day 2)	Predose, 2, 8 h	24 h (Day 2)	Predose, 2, 8 h	24 h (Day 9)	X
ABPM[e]		0-12 h	0-24 h				(Day 5-8)[e] 0-24 h			
ECG[f]	X	X		Predose, 2, 8 h	24 h (Day 2)	Predose		Predose, 2, 8 h	24 h (Day 9)	X
INR (PD and safety)[n]				Predose, 8 h[r]	24, 48, 72, 96 h			Predose, 8 h[r]	24, 48, 72, 96 h	
AEs & con meds[o]	Throughout study									
Bowel habit/dosing Patient diary		Daily from Baseline through the end of Cycle 2 (Period 4)								
Bowel habit Patient outcomes		X		Predose		Predose	Day7			
Abemaciclib Q12H						Day 1[k]	Day 2-7	Day 8[k]	Day 9-12	
Drug cocktail administration				X				X[s]		
PK sampling abemaciclib[g]							Predose (Day 7)	Predose	Predose (Day 9)	
PK sampling caffeine[g]				Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24, 48 h			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24, 48 h	
PK sampling warfarin[g,p]				Predose, 1, 2, 4, 6, 8, 10 h	24, 48, 72, 96 h			Predose, 1, 2, 4, 6, 8, 10 h	24, 48, 72, 96 h	

	Screen		Period 1: Drug cocktail			Period 2 (Cycle 1, Days 1-12): Abemaciclib + drug cocktail				Early discharge/ follow up[a]
Study Day	**≤ -30**	**Baseline ≤ -7**	**-1**	**1**	**2-7**	**1**	**2-7**	**8**	**9-12**	
PK sampling dextromethorphan[g]				Predose, 1, 2, 4, 6, 8, 10 h	24, 48, 72 h			Predose, 1, 2, 4, 6, 8, 10 h	24, 48, 72 h	
PK sampling midazolam[g]				Predose, 0.5, 1, 2, 3, 4, 6, 8,12 h	24 h			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24 h	
Pharmacogenetic sample		X[h]								
CYP genotyping sample		X[h]								
Tumor assessment	X[i]									

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; con meds = concomitant medications; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; exam = examination; INR = international normalized ratio; h = hour(s); PD = pharmacodynamic; PK = pharmacokinetic; Q12H = every 12 hours.

a Patients who discontinue early from the study should return for a discharge visit after a washout period of at least 10 days from the last abemaciclib dose to perform the same assessments as required at the follow-up visit. If a patient completes Periods 1 and 2, it is expected that the patient will enter Period 3. If patients do not enter Period 3 after completing required serial blood sampling in Period 2, patients will have a discharge visit after a washout period of at least 10 days from the last abemaciclib dose.

b Serum pregnancy test should be repeated if >3 days from Day 1.

c Directed physical examination. Directed examination on Day 9 to include assessment for evidence of bleeding.

d Vital signs will be collected before any blood samples at the specified time. Supine, semi-recumbent, or sitting blood pressure, heart rate, and body temperature will be obtained. Vital signs can be omitted, if already taken as part of routine standard of care on the day informed consent is taken.

e An ABPM device will be fitted for a 12-hour acclimation period between Days -7 to -2 in Period 1. Following the acclimation period, baseline ABPM assessments will be performed over a 24-hour period between Day -2 and dosing on Day 1 in Period 1. In Period 2, ABPM assessments will be performed over a 24-hour period once between Days 5 to 8; no other procedures should be performed during this ABPM assessment.

f Patients must be supine or semi-recumbent for approximately 5 to 10 minutes before ECG collection and remain supine or semi-recumbent but awake during ECG collection. ECGs should be collected prior to any blood draws scheduled at the same time point, and ECGs should preferably be collected before (rather than just after) meals. ECGs may be obtained at additional times, when deemed clinically necessary.

g All sample times are relative to the administration of the drug cocktail, except for the trough abemaciclib samples. PK sample collection times are nominal; actual times should be recorded. Separate blood samples, 2 mL each, will be collected for the drug concentration measurements of abemaciclib, caffeine, dextromethorphan, midazolam, and warfarin.

h Obtain only once after enrollment and eligibility is confirmed. This sample can be taken during the baseline visit or at Predose Period 1, Day 1 once eligibility is confirmed.

i Radiological tumor assessment can be omitted if prior scan is within approximately 4 weeks. See Section 8.3 for additional information.

j Serum creatinine only.

k The first dose of abemaciclib on Day 1 should take place at the study site. Patients will report to the study site on Day 8 and will be coadministered abemaciclib and the drug cocktail in the morning.

l Includes 2 blood samples collected for central laboratory assessment of renal markers in serum.
m To include the recording of the use of alcohol, tobacco, nicotine replacement therapy, and caffeine.
n If warfarin is not dosed in Period 2 cocktail, the INR sampling throughout Period 2 is not required; however, the INR may be assessed at the investigator's discretion for safety purposes.
o Patients will be provided with a paper diary in which to record the start and stop times of all AEs, new concomitant medications and medications taken as needed from the baseline visit until the end of Period 2.
p If warfarin is not dosed in Period 2 cocktail, the warfarin PK sampling throughout Period 2 is not required.
q Date and time of informed consent will be recorded.
r The 8-hour postdose sample may be drawn within ±2 hours (thus, at the 6 hour postdose or 10 hour postdose time point at the discretion of the site). The actual time of collection must be recorded.
s Cocktail may be administered without warfarin in Period 2 if patient has an INR >2 after receiving warfarin in Period 1 (Section7.2.1).

Study I3Y-MC-JPCB Study Schedule for Periods 3 and 4

Study Day	*Period 3* Cycle 1, Days 13-28	*Period 4*[a] Cycle 2	Follow-up[b]
Directed physical exam & ECOG status		X	X
Vital signs[c] & weight		X[c]	X
Renal biomarkers		Days 1, 14[f], 28	
Bowel habit/dosing Patient diary	X (Daily)	Daily (Days 1 through 28)[g]	
Bowel habit Patient outcomes	Days 14, 21	Days 1, 7, 14, 21, 28[d]	
Hematology & serum chemistry		Days 1, 14[f], 28	X
AEs & con meds	X	X	X
Abemaciclib Q12H	X	Daily	
Tumor assessment		X[e]	X

Abbreviations: AE = adverse event; con meds = concomitant medications; ECOG = Eastern Cooperative Oncology Group; exam = examination; Q12H = every 12 hours.

a Patients will be required to return to the site on Day 1 of each 28-day cycle (±4 days).

b For patients who will not participate in the safety extension, the follow-up assessment will occur approximately 10 days after the end of the second cycle.

c Vital signs will be collected before any blood samples at the specified time. Supine, semi-recumbent, or sitting blood pressure, heart rate, and temperature will be obtained.

d Cycle 2, Day 28 patient outcomes may be completed before any procedures on Day 1 of Cycle 3.

e Radiological tumor assessment should be performed on Day 28 (±14 days).

f Cycle 2, Day 14 labs (+/- 2 days).

g Patient diary will extend through the end of Period 4 if longer than 28 days.

Study I3Y-MC-JPCB Study Schedule for Safety Extension Phase

Study Day	Safety extension: abemaciclib[a]	Follow-up[b]
Directed physical exam & ECOG status	X	X
Vital signs[c] & weight	X	X
ECG[e]		X
Hematology, serum chemistry, & urinalysis	X	X
AEs & con meds	X	X
Abemaciclib administration	X	
Tumor assessment	X[d]	X

Abbreviations: AE = adverse event; con meds = concomitant medications; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; exam = examination.

a Patients will be required to return to the site on Day 1 of each 28-day cycle (±4 days).

b For patients participating in the safety extension, the follow-up assessment will occur approximately 10 days after the planned end of the last cycle.

c Vital signs will be collected before any blood samples at the specified time. Supine, semi-recumbent, or sitting blood pressure, heart rate, and temperature will be obtained.

d Radiological tumor assessment should be performed on Day 28 (±14 days). Imaging studies should be performed at the end of every 2 cycles (approximately every 4 to 8 weeks) up until 30 days after final abemaciclib dose, when another therapy is initiated, when there is disease progression, or when the patient dies per standard of care until objective progression is observed based on the efficacy measurement criteria described in Section 8.3. If a patient is discontinued from the study, repeat radiology may be omitted if progressive disease can be documented quantitatively with clinical measurements.

e Patients must be supine or semi-recumbent for approximately 5 to 10 minutes before ECG collection and remain supine or semi-recumbent but awake during ECG collection. ECGs should be collected prior to any blood draws scheduled at the same time point, and ECGs should preferably be collected before (rather than just after) meals. ECGs may be obtained at additional times, when deemed clinically necessary.

Attachment 2. Protocol JPCB Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a]
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total and direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils	Alanine aminotransferase
Lymphocytes	Aspartate aminotransferase
Monocytes	Gamma-glutamyl transpeptidase
Eosinophils	Blood urea nitrogen
Basophils	Creatinine
Platelets	Uric acid
	Calcium
Coagulation parameters[a, f]	Glucose, random
aPTT	Albumin
PT	Total protein
INR	Magnesium
	Phosphorus
	Chloride
Urinalysis[a]	Lactate dehydrogenase
Specific gravity	Osmolality
pH	
Protein	**Renal Biomarkers**[b]
Glucose	Cystatin-C [c]
Ketones	NGAL [c, d]
Blood	KIM-1 [d]
Urine leukocyte esterase	Creatinine [c, d]
	Serum Urine Pregnancy Test (females of child bearing potential only)
	CYP2C9, CYP2D6, CYP3A4, and CYP3A5 genotyping[e]

Abbreviations: RBC = red blood cells; WBC = white blood cells; aPTT = activated partial thromboplastin time, CYP = cytochrome P450; INR = international normalized ratio; KIM-1 = kidney injury molecule-1; NGAL = neutrophil gelatinase-associated lipocalin; PT = prothrombin time.

[a] Performed by local laboratory for safety management and the central laboratory for reporting purposes at all timepoint, except screening when only a local laboratory will be used.

[b] Performed by a central laboratory (not performed at screening).

[c] Venous blood samples will be collected for serum tests.

[d] Urine samples (at least 5 mL and up to 120 mL) will be collected and tested.

[e] Performed at baseline only

[f] Coagulation parameters need not be measured in Period 2 if warfarin is not included in the Period 2 drug cocktail.

Attachment 3. Protocol JPCB 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/CP or designee.

Hepatic Monitoring Tests

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

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

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

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

Attachment 4. Protocol JPCB Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

When contacting Lilly to report a SAE, please have the following information available:

Patient Demographics

- patient identification (number), sex, date of birth, origin, height, and weight

Study Identification

- full trial protocol number, investigator's name, investigator's number

Study Drug

- drug code or drug name, unit dose, total daily dose, frequency, route, start dose, cycle details, start date and last dose date (if applicable)

Adverse Event

- description, date of onset, severity, treatment (including hospitalization), action taken with respect to study drug, clinical significance, test and procedure results (if applicable)

Relationship to Study Drug & Protocol Procedures

Concomitant Drug Therapy

- indication, total daily dose, duration of treatment, start date, action taken

In Case of Death

- cause, autopsy finding (if available), date, relationship to study drug and protocol procedures.

Attachment 5. Protocol JPCB Eastern Cooperative Oncology Group (ECOG) Performance Status

Eastern Cooperative Oncology Group (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 performance of a light or sedentary nature, for example, light housework, 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 more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken et al. 1982.

Attachment 6. Protocol JPCB Sampling Summary

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

Protocol I3Y-MC-JPCB Sampling Summary (Periods 1 to 4)

Purpose	Maximum Amount per Sample (mL)	Maximum Number Samples	Maximum Total Amount (mL)
Screening tests (local lab)[a]	7.5	1	7.5
Serum pregnancy test, if applicable[b]	5	2	10
Clinical laboratory tests (local lab)[a]	7.5	10	75
Clinical laboratory tests (central lab)[a]	15	10	150
Renal markers	5	8	40
Safety and PD INR	2	12	24
Drug concentrations:			
Caffeine	2	22	44
Warfarin	2	22	44
Dextromethorphan	2	20	40
Midazolam	2	20	40
Abemaciclib	2	3	6
Pharmacogenetic sample	10	1	10
CYP genotyping sample	10	1	10
Catheter flush	1	18	18
Additional PK sampling, if applicable	3	5	15
Provision for unscheduled labs	-	-	30
Total			563.5
Total rounded for clinical purposes			570

Abbreviation: INR = international normalized ratio; PD = pharmacodynamic; PK = pharmacokinetic.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Blood volume may vary.

Attachment 7. Protocol Amendment I3Y-MC-JPCB(d) Summary Effects of Multiple Doses of Abemaciclib on the Pharmacokinetics of Cytochrome P450 (CYP) 1A2, CYP2C9, CYP2D6, and CYP3A Substrates (Caffeine, Warfarin, Dextromethorphan, and Midazolam) in Cancer Patients

Overview

Protocol I3Y-MC-JPCB [Effects of Multiple Doses of Abemaciclib on the Pharmacokinetics of Cytochrome P450 (CYP) 1A2, CYP2C9, CYP2D6, and CYP3A Substrates (Caffeine, Warfarin, Dextromethorphan, and Midazolam) in Cancer Patients] 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 of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- In order to explain how AEs and concomitant medications are to be recorded during the study, information regarding a paper diary to be issued to patients has been added.
- As INR is measured in order to monitor any adverse anticoagulant effects of warfarin, the protocol has been revised to allow any subject with INR >2 after the first dose of warfarin to receive abemaciclib once their INR has stabilized or returned to baseline, and for the patient to receive drug cocktail without warfarin in Period 2. Flexibility has been added regarding replacement of such patients to allow assessment of the impact of the missing warfarin PK data on the overall analysis, prior to the decision being made to replace the subject.
- The abemaciclib dose adjustment criteria have been amended and clarification given to the requirement for dose reduction following administration of white blood cell growth factors only.
- A ±2 hour window of flexibility has been allowed, if necessary, around the 8 hour postdose renal marker, hematology and serum chemistry, and INR sampling time point, in order to ensure samples can be analyzed on the day they are drawn.
- Minor clarifications have been added and minor typographical and formatting edits were made throughout the document for clarity and consistency.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

6.1.1. Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria during screening prior to ~~first dose of study drug~~enrollment.

6.1.2. Exclusion Criteria

[13] Have received treatment within 28 days of the initial dose of study drug with an investigational product (non-cancer-related therapies) or non-approved use of a drug or device (other than the study drug used in this study) or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

6.2. Summary of Study Design

This will be an open-label, 4-period, fixed-sequence study, followed by a safety extension phase, in patients with advanced and/or metastatic cancer.

The drug cocktail of 100 mg caffeine, 10 mg warfarin, 30 mg dextromethorphan, and 0.2 mg midazolam will be administered orally as a single dose on 2 occasions: Day 1 in Period 1, and in combination with abemaciclib on Day 8 of Period 2, after 7 days of 200 mg abemaciclib Q12H dosing. After completing Period 2, patients will continue to receive abemaciclib at a dose of 200 mg Q12H (or a modified dose) through the end of Periods 3 and 4, in 28-day cycles, and then may continue in a safety extension phase until discontinuation criteria are met. Patients who do not complete dosing and PK sampling through Period 2 may be replaced.

Patients will be provided with an electronic diary from the baseline visit through the end of Cycle 2 to record the time and date of abemaciclib administration, ~~any constipation or~~ anti-diarrhea medications taken, and bowel habits and any changes.

6.2.1. Safety Extension Phase

Patients who participate in the safety extension phase of the study will receive an abemaciclib dose of 200 mg Q12H (or modified dose as applicable) on a 28-day cycle until discontinuation criteria are met (eg, disease progression, death, or unacceptable toxicity (Section 6.3). If interruptions in dosing are required for significant periods of time (> 14 days) continuation of treatment with abemaciclib may be considered if felt to be in the best interest of the patient's care and upon discussion with the medical monitor. Tumor re-staging may be allowed and will be documented when necessary.

7.2.1. Dosing Schedule

Period 2

On Days 1 to 12, 4 × 50-mg capsules of abemaciclib will be administered orally in the morning and evening with approximately 240 mL of room temperature water, in a sitting position. Abemaciclib should be taken at approximately the same time each day. On Day 8, abemaciclib will be coadministered with 10 mL of 20-mg/mL caffeine citrate solution (100 mg caffeine), 2 × 5-mg tablets of warfarin, 2 × 15-mg liquid gel capsules of dextromethorphan, and 0.1 mL of 2-mg/mL midazolam syrup with approximately 240 mL of room temperature water, in a sitting position. On Day 8 (coadministration with the drug cocktail), patients should not consume food beginning 1 hour before and ending 1 hour after taking study drugs.

If a patient has an INR >2 after the first dose of warfarin, the patient may receive the drug cocktail without warfarin in Period 2 and receive abemaciclib once their INR has stabilized or returned to baseline.

If a patient misses or vomits a dose of abemaciclib, that dose should be omitted (see Section 7.6 for compliance). Patients will be asked to take each dose of study drug within +/- 2 hours of the planned dose time or consider the dose a missed dose.

Periods 3, 4 and Safety Extension Phase

From Cycle 1, Period 3 and on Days 1 to 28 in each cycle (Cycle 2 onwards), 4 × 50-mg capsule of abemaciclib will be taken orally in the morning and evening. Abemaciclib should be taken at approximately the same time each day.

A delay of ≤7 days in the start of a cycle (Day 1) for justifiable reasons (for example, inclement weather, holidays, or weekends) other than toxicity will be permitted and does not constitute a protocol violation. A delay of ≤14 days in the start of a cycle (Day 1) to allow for recovery from toxicity will be permitted and does not constitute a protocol violation. A longer delay may be allowed for the start of Cycle 1 (or Period 2), if necessary. In cases where Cycle 1 (abemaciclib dosing) is significantly delayed from tumor staging during screening, baseline staging may be repeated. If there is any question, this may be discussed with the study medical monitor.

Table JPCB.7.1. Toxicity Dose Adjustments and Delays of Abemaciclib for Study JPCB

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
~~Hematologic Toxicity~~ Neutropenia/thrombocytopenia Section 7.2.2.1	Grade 3 which lasts 7 days	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
~~Hematologic Toxicity~~ Neutropenia/thrombocytopenia Section 7.2.~~1~~2.1	Recurrent Grade 3 (on later cycle) which lasts 7 days	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose ~~**MUST**~~**MAY** be reduced by 1 dose level – investigator's discretion.
~~Hematologic Toxicity~~ Neutropenia/thrombocytopenia Section 7.2.~~1~~2.1	Grade 4 which lasts 3 days	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic toxicity: **Patient requires administration of white blood cell growth factors** Section 7.2.~~1~~2.1	Regardless of severity (Growth factors use according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of white 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 lead to the use of white blood cell growth factor.
Nonhematologic Toxicity (except diarrhea) Section 7.2.2.2.1	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MAY** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Nonhematologic Toxicity Section 7.2.2.2.1	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Section 7.2.2.2.2	Requires hospitalization or Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Section 7.2.2.2.2	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 24 hours to at least Grade 1	Dose **SHOULD** be suspended until toxicity resolves to at least Grade 1.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Diarrhea Section 7.2.2.2.2	Diarrhea recurs despite maximal supportive measures after resuming same dose level after initial Grade 2 diarrhea	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.

Abbreviation: ASCO = American Society of Clinical Oncology.

Note: MAY = per the investigator's clinical judgment; SHOULD = not mandatory but highly recommended; MUST = mandatory.

7.2.2.1. Hematologic Toxicity

If a patient experiences Grade 4 ~~hematologic toxicity~~neutropenia/thrombocytopenia, which lasts 3 days, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of abemaciclib must be reduced as outlined in Table JPCB.7.2.

If a patient experiences Grade 3 ~~hematologic toxicity~~neutropenia/thrombocytopenia, which lasts 7 days, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of abemaciclib may be reduced by 1 dose level. If the patient experiences a recurrent episode of Grade 3 ~~hematologic toxicity~~neutropenia/thrombocytopenia in a later cycle, which lasts 7 days, then dosing must be suspended (until the toxicity resolves to at least Grade 2 and the dose of abemaciclib ~~must~~may be reduced by 1 dose level.

If a patient requires administration of white blood cell growth factors, the dose of study drug must be suspended for at least 48 hours after the last dose of white blood cell growth factors was administered and until toxicity resolves to at least Grade 2, then reduced by 1 dose level, if a dose reduction for the specific event necessitating the use of the white blood cell growth factors has not already occurred.

Before the start of each cycle, hematologic toxicity possibly related to abemaciclib must resolve to at least Grade 2.

7.5. Concomitant Therapy

No other chemotherapy, radiotherapy, immunotherapy, cancer-related hormone therapy, or experimental drugs will be permitted while the patients are on this study, except for those described in Inclusion Criterion [7] in Section 6.1.1.

The need for radiotherapy will be cause for early discontinuation from the study, with the exception of palliative radiotherapy, which is permitted if not being utilized for disease progression. In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study.

Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the case report form (CRF). Patients will be provided with a paper diary in which to record the start and stop times of new concomitant medications and medications taken as needed from the baseline visit until the end of Period 2.

7.5.1.3. Growth Factors

Patients should receive full supportive care during the trial. Growth factors should not be administered to enable a patient to satisfy study inclusion criteria. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2015) if clinically indicated. Dosing of study drug must be suspended if the administration of white blood cell 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 white blood cell growth factors, the dose of study drug must be reduced by one dose level, if a dose reduction for the specific event necessitating the use of the growth factors has not already

occurred. Before the start of each cycle, hematologic toxicity must resolve to either baseline or at least Grade 2.

Erythroid-stimulating agents (ESAs, including erythropoietin and darbepoetin) or transfusions should not be administered to enable a patient to satisfy study inclusion criteria. Both ESAs and transfusion therapy may be used in accordance with American Society of Hematology and ASCO guidelines (Rizzo et al. 2010), if clinically indicated. ~~If a patient requires administration of blood cell growth factors, the dose of study drug must be reduced by one dose level, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred. Before the start of each cycle, hematologic toxicity must resolve to either baseline or at least Grade 2.~~

7.6 Treatment Compliance

If a patient misses 2 or more of the planned doses of abemaciclib within 3 consecutive days prior to the drug cocktail dose in Period 2, the patient will need to be replaced, or dosing with the drug cocktail may be delayed to allow for adequate exposure. Delay should only occur on a case-by-case basis following discussion and agreement with the Lilly CRP/CP or designee. Likewise, if dose reduction is required to less than 150mg Q12H or if dose interruptions or omissions are deemed necessary during Period 2 for greater than 4~~3~~ consecutive doses at any time, the patient may recommence dosing of abemaciclib with delay of Period 2 drug cocktail dosing so that abemaciclib steady state is achieved (~~minimum~~ 5-7 days)~~will need to be replaced~~.

8.1.2. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which 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 medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any clinically significant findings from labs, vital sign measurements, and so on that occur should also be reported to Lilly or its designee as an AE. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

The investigator, monitor, and sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the Study Schedule. Patients will be provided with a paper diary in which to record the start and stop times of all AEs experienced from the baseline visit until the end of Period 2.

8.1.3.1. Vital Signs

Blood pressure, pulse rate, and body temperature will be measured as specified in the Study Schedule and as clinically indicated (Attachment 1).

Blood pressure and pulse rate should be measured after at least 5 minutes supine ~~or~~, semi-recumbent, or sitting; the position should be recorded.

8.1.3.3. Electrocardiograms

For each patient, a 12-lead digital ECG will be collected according to the Study Schedule (Attachment 1). Patients must be supine or semi-recumbent for approximately 5 to 10 minutes before ECG collection and remain supine or semi-recumbent but awake during ECG collection.

8.1.3.4.2. Patient Diary

An electronic patient diary to collect date and time of bowel movements, a Bristol Stool Chart, and drug administration will be completed daily by the patient, starting at baseline and required through end of Period 2. Patients participating in Period 3 and 4 should continue completing diary entries through end of Period 4. Patients will also receive a paper diary in which to record the start and stop times of all AEs, new concomitant medications and medications taken as needed from the baseline visit until the end of Period 2.

8.2.2.2. Pharmacodynamic Samples

At the visits and times specified in the Study Schedule (Attachment 1), venous blood samples will be collected to determine INR (see Attachment for the blood sampling summary). Analysis of PT or INR will be performed by local labs. Local labs for PT or INR will be collected for patient management and PD analyses.

Guidance Regarding Elevation of the INR

Patients will receive a single dose of warfarin (10 mg) as part of the drug cocktail in Period 1 and Period 2:

> Period 1: If a patient has an INR >2 after the first dose of warfarin, the patient should not receive warfarin again in the drug cocktail in Period 2, but may be allowed to enter ~~the study~~Period 2 and receive abemaciclib once their INR has stabilized or returned to baseline. The patient ~~should~~ may be replaced.
>
> Period 2: For any patient found to have an INR ≥4 after the administration of warfarin in Period 2, further abemaciclib dosing should be held until the INR stabilizes or returns to baseline (refer to Section7.2.2).

9.2.1 Case Report Form

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

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome measures (for example, a rating scale), a daily dosing schedule or an event diary.

If information reported during an office visit differs from that recorded in the paper diaries, the source data (collected during patient interview) will supersede for purposes of collection in the CRF.

For data handled by a data management third-party organization (TPO), CRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the Lilly data warehouse, using standard Lilly file transfer processes.

11.1. Informed Consent

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

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

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

Study I3Y-MC-JPCB Study Schedule for Screening, and Periods 1 and 2

	Screen		Period 1: Drug cocktail			Period 2 (Cycle 1, Days 1-12): Abemaciclib + drug cocktail				Early discharge/ follow up[a]
Study Day	**≤ -30**	**Baseline ≤ -7**	**-1**	**1**	**2-7**	**1**	**2-7**	**8**	**9-12**	
Informed consent	X[q]									
Medical history[m]	X									
Pregnancy test (if applicable)	X	X[b]								
Urinalysis	X	X[b]			X (Day 7)				X (Day 9)	X
Renal markers				Predose[l]				Predose 8 h[r]	24, 72 h (Days 9, 11)	
Hematology and serum chemistry	X	X[b]			X (Day 7)			Predose, 8h[j,r]	24, 72 h (Days 9, 11)	X
Physical exam & ECOG status	X	X[b,c]				Predose[c]			24 h (Day 9)[c]	X[c]
Weight	X	X				X				X
Vital signs[d]	X	X[b]		Predose, 2, 8 h	24 h (Day 2)	Predose, 2, 8 h	24 h (Day 2)	Predose, 2, 8 h	24 h (Day 9)	X
ABPM[e]		0-12 h	0-24 h				(Day 5-8)[e] 0-24 h			
ECG[f]	X	X		Predose, 2, 8 h	24 h (Day 2)	Predose		Predose, 2, 8 h	24 h (Day 9)	X
INR (PD and safety)[n]				Predose, 8 h[r]	24, 48, 72, 96 h			Predose, 8 h[r]	24, 48, 72, 96 h	
AEs & con meds[o]	Throughout study									
Bowel habit/dosing Patient diary		Daily from Baseline through the end of Cycle 2 (Period 4)								
Bowel habit Patient outcomes		X		Predose		Predose	Day7			
Abemaciclib Q12H						Day 1[k]	Day 2-7	Day 8[k]	Day 9-12	
Drug cocktail administration				X				X[s]		
PK sampling abemaciclib[g]							Predose (Day 7)	Predose	Predose (Day 9)	
PK sampling caffeine[g]				Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24, 48 h			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24, 48 h	
PK sampling warfarin[g,p]				Predose, 1, 2, 4, 6, 8, 10 h	24, 48, 72, 96 h			Predose, 1, 2, 4, 6, 8, 10 h	24, 48, 72, 96 h	

	Screen		Period 1: Drug cocktail			Period 2 (Cycle 1, Days 1-12): Abemaciclib + drug cocktail				Early discharge/ follow up[a]
Study Day	**≤ -30**	**Baseline ≤ -7**	**-1**	**1**	**2-7**	**1**	**2-7**	**8**	**9-12**	
PK sampling dextromethorphan[g]				Predose, 1, 2, 4, 6, 8, 10 h	24, 48, 72 h			Predose, 1, 2, 4, 6, 8, 10 h	24, 48, 72 h	
PK sampling midazolam[g]				Predose, 0.5, 1, 2, 3, 4, 6, 8,12 h	24 h			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24 h	
Pharmacogenetic sample		X[h]								
CYP genotyping sample		X[h]								
Tumor assessment	X[i]									

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; con meds = concomitant medications; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; exam = examination; INR = international normalized ratio; h = hour(s); PD = pharmacodynamic; PK = pharmacokinetic; Q12H = every 12 hours.

a Patients who discontinue early from the study should return for a discharge visit after a washout period of at least 10 days from the last abemaciclib dose to perform the same assessments as required at the follow-up visit. If a patient completes Periods 1 and 2, it is expected that the patient will enter Period 3. If patients do not enter Period 3 after completing required serial blood sampling in Period 2, patients will have a discharge visit after a washout period of at least 10 days from the last abemaciclib dose.

b Serum pregnancy test should be repeated if >3 days from Day 1.

c Directed physical examination. Directed examination on Day 9 to include assessment for evidence of bleeding.

d Vital signs will be collected before any blood samples at the specified time. Supine ~~or,~~ semi-recumbent, or sitting blood pressure, heart rate, and body temperature will be obtained. Vital signs can be omitted, if already taken as part of routine standard of care on the day informed consent is taken.

e An ABPM device will be fitted for a 12-hour acclimation period between Days -7 to -2 in Period 1. Following the acclimation period, baseline ABPM assessments will be performed over a 24-hour period between Day -2 and dosing on Day 1 in Period 1. In Period 2, ABPM assessments will be performed over a 24-hour period once between Days 5 to 8; no other procedures should be performed during this ABPM assessment.

f Patients must be supine or semi-recumbent for approximately 5 to 10 minutes before ECG collection and remain supine or semi-recumbent but awake during ECG collection. ECGs should be collected prior to any blood draws scheduled at the same time point, and ECGs should preferably be collected before (rather than just after) meals. ECGs may be obtained at additional times, when deemed clinically necessary.

g All sample times are relative to the administration of the drug cocktail, except for the trough abemaciclib samples. PK sample collection times are nominal; actual times should be recorded. Separate blood samples, 2 mL each, will be collected for the drug concentration measurements of abemaciclib, caffeine, dextromethorphan, midazolam, and warfarin.

h Obtain only once after enrollment and eligibility is confirmed. This sample can be taken during the baseline visit or at Predose Period 1, Day 1 once eligibility is confirmed.

i Radiological tumor assessment can be omitted if prior scan is within approximately 4 weeks. See Section 8.3 for additional information.

j Serum creatinine only.

k The first dose of abemaciclib on Day 1 should take place at the study site. Patients will report to the study site on Day 8 and will be coadministered abemaciclib and the drug cocktail in the morning.

l Includes 2 blood samples collected for central laboratory assessment of renal markers in serum.
m To include the recording of the use of alcohol, tobacco, nicotine replacement therapy, and caffeine.
n If warfarin is not dosed in Period 2 cocktail, the INR sampling throughout Period 2 is not required; however, the INR may be assessed at the investigator's discretion for safety purposes.
o Patients will be provided with a paper diary in which to record the start and stop times of all AEs, new concomitant medications and medications taken as needed from the baseline visit until the end of Period 2.
p If warfarin is not dosed in Period 2 cocktail, the warfarin PK sampling throughout Period 2 is not required.
q Date and time of informed consent will be recorded.
r The 8-hour postdose sample may be drawn within ±2 hours (thus, at the 6 hour postdose or 10 hour postdose time point at the discretion of the site). The actual time of collection must be recorded.
s Cocktail may be administered without warfarin in Period 2 if patient has an INR >2 after receiving warfarin in Period 1 (Section 7.2.1).

Study I3Y-MC-JPCB Study Schedule for Periods 3 and 4

Study Day	*Period 3* Cycle 1, Days 13-28	*Period 4*[a] Cycle 2	Follow-up[b]
Directed physical exam & ECOG status		X	X
Vital signs[c] & weight		X[c]	X
Renal biomarkers		Days 1, 14[f], 28	
Bowel habit/dosing Patient diary	X (Daily)	Daily (Days 1 through 28)[g]	
Bowel habit Patient outcomes	Days 14, 21	Days 1, 7, 14, 21, 28[d]	
Hematology & serum chemistry		Days 1, 14[f], 28	X
AEs & con meds	X	X	X
Abemaciclib Q12H	X	Daily	
Tumor assessment		X[e]	X

Abbreviations: AE = adverse event; con meds = concomitant medications; ECOG = Eastern Cooperative Oncology Group; exam = examination; Q12H = every 12 hours.

a Patients will be required to return to the site on Day 1 of each 28-day cycle (±4 days).

b For patients who will not participate in the safety extension, the follow-up assessment will occur approximately 10 days after the end of the second cycle.

c Vital signs will be collected before any blood samples at the specified time. Supine, ~~or~~ semi-recumbent, or sitting blood pressure, heart rate, and temperature will be obtained.

d Cycle 2, Day 28 patient outcomes may be completed before any procedures on Day 1 of Cycle 3.

e Radiological tumor assessment should be performed on Day 28 (±14 days).

f Cycle 2, Day 14 labs (+/- 2 days).

g Patient diary will extend through the end of Period 4 if longer than 28 days.

Study I3Y-MC-JPCB Study Schedule for Safety Extension Phase

Study Day	Safety extension: abemaciclib[a]	Follow-up[b]
Directed physical exam & ECOG status	X	X
Vital signs[c] & weight	X	X
ECG[e]		X
Hematology, serum chemistry, & urinalysis	X	X
AEs & con meds	X	X
Abemaciclib administration	X	
Tumor assessment	X[d]	X

Abbreviations: AE = adverse event; con meds = concomitant medications; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; exam = examination.

[a] Patients will be required to return to the site on Day 1 of each 28-day cycle (±4 days).

[b] For patients participating in the safety extension, the follow-up assessment will occur approximately 10 days after the planned end of the last cycle.

[c] Vital signs will be collected before any blood samples at the specified time. Supine, ~~or~~ semi-recumbent, or sitting blood pressure, heart rate, and temperature will be obtained.

[d] Radiological tumor assessment should be performed on Day 28 (±14 days). Imaging studies should be performed at the end of every 2 cycles (approximately every 4 to 8 weeks) up until 30 days after final abemaciclib dose, when another therapy is initiated, when there is disease progression, or when the patient dies per standard of care until objective progression is observed based on the efficacy measurement criteria described in Section 8.3. If a patient is discontinued from the study, repeat radiology may be omitted if progressive disease can be documented quantitatively with clinical measurements.

[e] Patients must be supine or semi-recumbent for approximately 5 to 10 minutes before ECG collection and remain supine or semi-recumbent but awake during ECG collection. ECGs should be collected prior to any blood draws scheduled at the same time point, and ECGs should preferably be collected before (rather than just after) meals. ECGs may be obtained at additional times, when deemed clinically necessary.

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a]
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total and direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils	Alanine aminotransferase
Lymphocytes	Aspartate aminotransferase
Monocytes	Gamma-glutamyl transpeptidase
Eosinophils	Blood urea nitrogen
Basophils	Creatinine
Platelets	Uric acid
	Calcium
Coagulation parameters[a, f]	Glucose, random
aPTT	Albumin
PT	Total protein
INR	Magnesium
	Phosphorus
	Chloride
Urinalysis[a]	Lactate dehydrogenase
Specific gravity	Osmolality
pH	
Protein	**Renal Biomarkers**[b]
Glucose	Cystatin-C [c]
Ketones	NGAL [c, d]
Blood	KIM-1 [d]
Urine leukocyte esterase	Creatinine [c, d]
	Serum Urine Pregnancy Test (females of child bearing potential only)
	CYP2C9, CYP2D6, CYP3A4, and CYP3A5 genotyping[e]

Abbreviations: RBC = red blood cells; WBC = white blood cells; aPTT = activated partial thromboplastin time, CYP = cytochrome P450; INR = international normalized ratio; KIM-1 = kidney injury molecule-1; NGAL = neutrophil gelatinase-associated lipocalin; PT = prothrombin time.

a Performed by local laboratory for safety management and the central laboratory for reporting purposes at all timepoint, except screening when only a local laboratory will be used.

b Performed by a central laboratory (not performed at screening).

c Venous blood samples will be collected for serum tests.

d Urine samples (at least 5 mL and up to 120 mL) will be collected and tested.

e Performed at baseline only

f Coagulation parameters need not be measured in Period 2 if warfarin is not included in the Period 2 drug cocktail.

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