Protocol I3Y-CR-JPBR (e)

A Phase 1 Study of Abemaciclib in Native Chinese Patients with Advanced and/or Metastatic Cancers

NCT02919696

Approval Date: 12-Apr-2019

1. Protocol I3Y-CR-JPBR(e)
A Phase 1 Study of Abemaciclib in Native Chinese Patients with Advanced and/or Metastatic Cancers

Confidential Information

Abemaciclib (LY2835219)

This Phase 1 study is a multicenter, randomized, open-label study of oral abemaciclib in native Chinese patients with advanced and/or metastatic cancers.

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Protocol Electronically Signed and Approved by Lilly: 22 April 2016
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2. Synopsis

This Phase 1 study is a multicenter, randomized, open-label study of oral abemaciclib in Chinese patients with advanced and/or metastatic cancers.

Abemaciclib is a selective and potent small molecule cyclin-dependent kinase (CDK) 4/6 dual inhibitor with antitumor activity that is being developed for the treatment of cancers. The objective of this study is to evaluate safety and tolerability of abemaciclib in Chinese patients with advanced and/or metastatic cancers.

Clinical Protocol Synopsis: Study I3Y-CR-JPBR

Name of Investigational Product: abemaciclib	
Title of Study: A Phase 1 Study of Abemaciclib in Native Chinese Patients with Advanced and/or Metastatic Cancers	
Number of Planned Patients: 20	**Phase of Development:** 1
Length of Study: Planned first patient visit: 17 April 2017 Planned last patient visit: 4 May2018 (End of trial is defined as the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study.)	
Objectives: The primary objective of this study is to evaluate the safety and tolerability of abemaciclib in Chinese patients with advanced and/or metastatic cancers. The secondary objectives of this study are as follows: • To assess the pharmacokinetics (PK) of abemaciclib and its metabolites in Chinese patients with advanced and/or metastatic cancers • To assess the antitumor activity of abemaciclib	
Study Design: This study is a multicenter, open-label, Phase 1 trial of abemaciclib in Chinese patients with advanced and/or metastatic cancers. The study will be focused on safety evaluation and PK data collection in patients with all advanced and/or metastatic cancers. Patients will be randomized into 2 dose cohorts, and orally receive abemaciclib 150 mg or 200 mg every 12 hours (Q12H). One cycle is defined as 28 days (Cycle 1: 32 days), with modifications during Cycle 1 to enable PK sampling following a single dose and repeated doses. The treatment of abemaciclib will continue until disease progression, development of unacceptable toxicity, or fulfillment of the other discontinuation criteria. In case of patient discontinuation during Cycle 1, the enrollment will be extended until at least 10 patients with completed PK data are accrued in each cohort. Analysis on available PK and safety data will be conducted after study completion. All patients in the study receive at least 2 cycles of abemaciclib unless one or more of the criteria for discontinuation are fulfilled; the short-term follow-up period for poststudy evaluation is 30 ±7 days after the decision to discontinue treatment.	
Diagnosis and Criteria for Inclusion and Exclusions: **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. [1] The patient must have histological or cytological evidence of cancer which is advanced and/or metastatic, and is an appropriate candidate for experimental therapy in the judgment of the investigator, after available standard therapies have ceased to provide clinical benefit. [2] Have the presence of measureable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).	

[3] This criterion has been deleted.
[4] This criterion has been deleted.
[5] This criterion has been deleted.
[6] Are native Chinese men or women≥18 years of age.
[7] Have given written informed consent prior to any study-specific procedures.
[8] Have adequate organ function, including:
- Hematologic: Absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, and hemoglobin≥9 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level or platelet transfusions to achieve platelet levels at the discretion of the investigator; however, initial study drug treatment must not begin earlier than the day after transfusion.
- Hepatic: Bilirubin ≤1.5 times upper limits of normal (ULN), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3.0 times ULN.
- Renal: Serum creatinine ≤1.2 mg/dL for males or ≤1.0 mg/dL for females.

[9] Have a performance status ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale.
[10] Recovered from the acute effects of therapy (treatment- related toxicity resolved to baseline) except for residual alopecia.
[11] Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.
[12] Males and females with reproductive potential must agree to use medically approved precautions to avoid pregnancy during the trial and for 3 months following the last dose of study drug.
[9a] Are a man and agree to use a reliable method of birth control and to not donate sperm during the study and for at least 3 months following the last dose of study drug, OR
[9b] Are a woman of child-bearing potential with a negative serum pregnancy test at baseline (within 7 days prior to randomization and agree to use a reliable method of birth control during the study and for 3 months following the last dose of the study drug.
A woman of child-bearing potential is defined as a premenopausal female. A postmenopausal female is defined as a woman:
1) at least 6 weeks after surgical bilateral oophorectomy that can be confirmed on medical history records, OR
2) with spontaneous amenorrhea for at least 12 months, not induced by a medical conditions such as anorexia nervosa nor induced by medication.
[13] Have an estimated life expectancy of ≥12 weeks.
[14] Are able to swallow capsules.

Exclusion Criteria

Potential study patients may not be included in the study if any of the following apply during screening.
[15] Have received previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and investigational therapy) within 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents prior to receiving study drug.
[16] Have a personal history of any of the following conditions: presyncope or syncope of either unexplained or cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest, or have a baseline ECG with any of the following abnormal findings: ventricular arrhythmia, evidence of acute myocardial ischemia, heart block (of any degree), or QTc prolongation (defined as QTcB ≥450 milliseconds).
[17] Have serious 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).
[18] Have an acute leukemia or other relevant cancers at the discretion of the investigator.
[19] Females who are pregnant or lactating.
[20] Have active bacterial, fungal, and/or known viral infection (for example, human immunodeficiency virus [HIV] antibodies, hepatitis B surface antigen [HBSAg], or hepatitis C antibodies). Screening for active infections is not required for enrollment.

[21] Patients consuming drugs or foods that are known to be inducers (for example, grapefruit juice, phenytoin, carbamazepine) or strong inhibitors of CYP3A4 should be excluded during Cycle 1.
[22] Patients receiving herbal regimens during Cycle 1 should be excluded.
[23] Have history or evidence of central nervous system (CNS) malignancy or metastasis. Screening of asymptomatic patients without history of CNS metastases is not required for enrollment.
[24] This criterion has been deleted.

Investigational Product, Dosage, and Mode of Administration:
Oral abemaciclib will be administered Q12H, and at approximately the same time each day on a 28-day cycle except Cycle 1.

- The initial dose of study drug in Cycle 1 will be taken on Day 1 to enable PK sampling over 72 hours following a single dose; the remaining 55 doses will be taken every 12 hours on Days 4 to 31, with PK sampling on Day 18, Day 25 and over 24 hours following the single dose taken on Day 31. Patients should be specifically instructed not to take a second dose of study drug on Day 31.
- In Cycle 2 and beyond, study drug will be taken every 12 hours on Days 1 through 28 of a 28-day cycle.

Planned Duration of Treatment:
Patients will be on treatment until one of the discontinuation criteria is met.

Criteria for Evaluation:
Safety:
Hematology, chemistry, treatment-emergent adverse events (TEAEs) using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 and the Medical Dictionary for Regulatory Activities (MedDRA), serious adverse events (SAEs), dose adjustments, electrocardiogram (ECG) and vital signs.

Efficacy:
Antitumor activity according to RECIST v. 1.1.

Bioanalytical:
Plasma concentrations of abemaciclib and its major metabolites LSN2839567 (M2) and LSN3106726 (M20) will be determined using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

Pharmacokinetic:
Maximum plasma concentration (C_{max}), area under the plasma concentration versus time curve ($AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$), and the time of maximal plasma concentration (t_{max}) following single and multiple dose. In addition, half-life ($t_{1/2}$), apparent volume of distribution (V/F), apparent systemic clearance (CL/F) and other relevant parameters.

Statistical Methods:
Safety: Adverse events (AEs) including dose-limiting toxicity (DLT)-equivalent toxicities and TEAEs will be listed and summarized in frequency tables. Severity of AE will be classified using CTCAE Version 4.0. Other safety data such as laboratory tests and vital signs, will be summarized using summary statistics.

Efficacy: Efficacy data will be listed by tumor type.

Pharmacokinetic: The PK parameters of abemaciclib and its metabolites will be computed by standard noncompartmental methods of analysis using Phoenix WinNonlin.

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
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
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
$AUC_{(0\text{-}tlast)}$	area under the plasma concentration-time curve from time zero to last measurable plasma concentration
$AUC_{(0\text{-}\infty)}$	area under the plasma concentration-time curve from time zero to infinity
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
CDKI	cyclin-dependent kinase inhibitors
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent systemic clearance
CLRM	Clinical Laboratory Results Modernization
C_{max}	maximum plasma 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.
CR	complete response
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.
CRP	clinical research physician
CRS	clinical research scientist
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
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.
FAS	full analysis set
FFPE	formalin-fixed paraffin-embedded

FNA	fine needle aspirate
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factors
HBSAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC50	50% inhibition concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
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.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.
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.
IV	intravenous
IWRS	interactive web response system
LC/MS/MS	liquid chromatography with tandem mass spectrometry
mBC	metastatic breast cancer
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
monitor	A person responsible for ensuring the investigator site complies with the monitoring plan, applicable local SOPs (if any), and global Medical SOPs. Monitors are trained on the investigational product(s), the protocol, informed consent document, any other written information provided to subjects, relevant SOPs, International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP), and all applicable laws (for example, privacy and data protection) and regulations.
MRI	magnetic resonance imaging

MTD	maximum tolerated dose
NCI	National Cancer Institute
NSAI	nonsteroidal aromatase inhibitors
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.
ORR	objective response rate
OS	overall survival
patient	A subject with a defined disease.
PD	progressive disease
PFS	progression-free survival
pHH3	phospho-histone H3
PK	pharmacokinetic
PR	partial response
pRb	phosphorylated retinoblastoma protein
Q12H	every 12 hours
Q24H	every 24 hours
QTc	corrected QT interval
Rb	retinoblastoma protein
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
SAP	Statistical Analysis Plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial.
screen failure	A patient who does not meet one or more criteria required for participation in a

	trial
SD	stable disease
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
TEAE	treatment-emergent adverse event
TED_{70}	threshold effective dose for 70% inhibition
TGI	tumor growth inhibition
t_{max}	time of maximal plasma concentration
topoIIα	topoisomerase II alpha
TPO	third-party organization
ULN	upper limit of normal
V/F	apparent volume of distribution
VPCs	ventricular premature complexes
VT	ventricular tachycardia
VTE	venous thromboembolic event
WBC	white blood cells

A Phase 1 Study of Abemaciclib in Native Chinese Patients with Advanced and/or Metastatic Cancers

5. Introduction

5.1. Rationale and Justification for the Study

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for maintaining control of cell division (Ortega et al. 2002; Sherr 1996). The cyclin-dependent kinases, CDK4 and CDK6 (hereafter designated CDK4/6), participate in a complex with D-type cyclins to initiate the transition through the G1 restriction point. A broad spectrum of human cancers have alterations in the CDK4/6-cyclinD-INK4-Rb pathway through either increased CDK4/6-cyclinD activity or mutations that attenuate function of the INK4 or Rb (retinoblastoma) proteins (Malumbres and Barbacid 2001). These alterations render cells less dependent on mitogenic signaling for proliferation, one of the hallmarks of cancer cells.

The CDK4/6-cyclinD1 complex regulates the G1 restriction point through phosphorylation of the Rb tumor suppressor protein. Alterations in this pathway occur frequently in a broad spectrum of human cancers and involve 1) loss of cyclin-dependent kinase inhibitors (CDKI) by mutation or epigenetic silencing, 2) mutation/overexpression of either CDK4/6 or cyclin D, or 3) inactivation of Rb. With the possible exception of those tumors with complete inactivation of Rb, which functions downstream of the CDK4/6-cyclinD1 complex, all these cancers are potentially sensitive to pharmacologic inhibition of CDK4/6. From a therapeutic standpoint, the goal of inhibiting CDK4/6 with a small molecule inhibitor is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

Abemaciclib is a selective and potent small molecule CDK4/6 dual inhibitor with antitumor activity in preclinical pharmacology models, acceptable physical and pharmacokinetic (PK) properties, and an acceptable toxicity profile in nonclinical species. This compound demonstrates significant inhibition of tumor growth in multiple human xenograft models including colorectal cancer, glioblastoma multiforme, acute myeloid leukemia, and non–small cell lung cancer (NSCLC). Although characterized by a different constellation of genomic mutations, each of these 4 human xenografts has an intact, functional Rb protein. Xenograft growth inhibition is generally dose dependent from 25 to 100 mg/kg following daily oral administration for 21 to 28 days.

The Phase 1 first-in-human study I3Y-MC-JPBA (Study JPBA) established a maximum tolerated dose (MTD: 200 mg every 12 hours on Days 1 through 28 of a 28-day cycle) and demonstrated acceptable safety and tolerability for abemaciclib in patients with advanced and/or metastatic cancers. In this trial, abemaciclib demonstrated early single-agent clinical activity in cancers. Study I3Y-JE-JPBC (Study JPBC) was a 3-cohort dose-escalation Phase 1 trial in Japanese patients with advanced and/or metastatic cancers designed to confirm the safety and tolerability of abemaciclib up to the MTD which was established in Study JPBA.

Based on the Study JPBA expansion cohort of 68 patients with advanced and/or metastatic NSCLC, a global multicenter, open-label, randomized Phase 3 trial, I3Y-MC-JPBK (Study JPBK), is ongoing to compare the efficacy and safety of abemaciclib (200 mg Q12H) with erlotinib treatment for patients with Stage IV NSCLC whose tumors have a detectable KRAS mutation in either Codon 12 or 13 as detected by an investigational assay and who have progressed after platinum-based chemotherapy.

Based on the other Study JPBA expansion cohort of 47 patients with metastatic breast cancer (mBC), a multicenter, randomized, Phase 3 study, Study I3Y-CR-JPBQ (JPBQ), is planned to compare the efficacy and safety to nonsteroidal aromatase inhibitors (NSAI) plus abemaciclib (150 mg Q12H) or plus placebo, and to compare fulvestrant plus abemaciclib (150 mg Q12H) or plus placebo in mainly east Asian postmenopausal women with hormone receptor-positive, HER2-negative locoregionally recurrent or metastatic breast cancer.

This Phase 1 trial, Study I3Y-CR-JPBR (hereafter Study JPBR), is designed to evaluate the safety and tolerability of abemaciclib monotherapy in Chinese patients with advanced and/or metastatic cancers to support Phase 3 studies to be conducted in China.

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

5.2. Objectives

5.2.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of abemaciclib in Chinese patients with advanced and/or metastatic cancers.

5.2.2. Secondary Objectives

The secondary objectives of this study are:

- to assess the PK of abemaciclib and its metabolites in Chinese patients with advanced and/or metastatic cancers
- to assess the antitumor activity of abemaciclib

5.3. General Introduction to Abemaciclib

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. Mechanism of Action and In Vitro/In Vivo Activity

Abemaciclib represents a novel class of potent adenosine triphosphate (ATP) competitive and reversible CDK4/6 kinase inhibitor (50% inhibition concentration [IC50] for CDK4 = 0.00196 μM and IC50 for CDK6 = 0.0099 μM). This molecule displays a high level of selectivity over other related cyclin-dependent kinases at the enzyme and cellular level; for example, abemaciclib is approximately 3 orders of magnitude more selective for CDK4 compared to CDK1. In Colo-205 cells, the compound induces potent cellular inhibition of Rb phosphorylation (pSer780, IC50 = 0.121 μM). Other data has demonstrated that abemaciclib inhibits CDK4/6 to induce G1 arrest specifically in Rb+ tumors and is selective for G1 arrest at concentrations as high as 2.5 to 6 μM.

This phenotypic selectivity is also demonstrated *in vivo*, where LSN2813542 (that is, abemaciclib mesylate) suppresses Rb phosphorylation and induces a G1 arrest as indicated by inhibition of topoisomerase II alpha and phospho-histone H3 (topoIIα and pHH3 markers respectively, for cells in S phase and M phase), in a concerted fashion only consistent with arrest at the G1 restriction point *in vivo*. Additionally, LSN2813542 showed excellent, sustained pharmacodynamic response in a mouse Colo-205 xenograft model (*in vivo* pRb inhibition ≥50% from 1 to 36 hours post oral dose of 50 mg/kg and potent suppression of topoIIα and pHH3 at 24 hours post oral dose of the same 50-mg/kg dose). Dose response TED_{70} (threshold effective dose for 70% inhibition) values for pRb and topoIIα inhibition (24 hours post oral dose time point) were 14.1 and 14.3 mg/kg, respectively. This prolonged, robust target inhibition and G1 arrest has resulted in the demonstration of statistically significant, dose-dependent antitumor activities (measured by tumor volume reduction) of LSN2813542 in 4 human subcutaneous xenograft models: Colo-205 colorectal, H460 lung, U87 MG glioblastoma multiforme and MV4-11 acute myeloid leukemia. For example, LSN2813542 can achieve statistically significant tumor growth inhibition when dosed orally at 25, 50, and 100 mg/kg for 21 days in the Colo-205 xenograft model. Consistent with the mechanism of action of LSN2813542, the antitumor activity in Colo-205 was associated with a sustained inhibition of pRb, topoIIα and pHH3 (30% to 50% inhibition of each marker on Days 14 and 21 of dosing at 100 mg/kg).

As a result of its brain exposure, treatment with this compound produces a statistically significant and dose-dependent improvement in survival in a rat orthotopic brain tumor model. Median survival was improved 8 and 12 days compared to vehicle following daily oral treatment at 40 mg/kg and 80 mg/kg for 21 days, respectively.

5.3.2. Nonclinical Pharmacokinetics

Studies evaluating absorption, distribution, metabolism, and excretion of abemaciclib were conducted in rats and dogs. A single oral dose of radiolabeled abemaciclib was slowly absorbed (t_{max} ranged from 6.7 to 8 hours for abemaciclib and 8 hours for radioactivity), with parent drug accounting for approximately 79% and 41% of the plasma radioactivity in rats and dogs, respectively. The radioactivity associated with [^{14}C]abemaciclib was extensively distributed to tissues and organs in both pigmented (Long Evans) and nonpigmented (Sprague Dawley) rats and was selectively associated with melanin-containing tissues. Radioactivity in central nervous

system (CNS) tissues protected by the blood-brain barrier (cerebellum, cerebrum, medulla, and spinal cord) was measurable through 24 hours postdose. Plasma protein binding of abemaciclib was high (mean ranged from approximately 95% to 99%) across species and its active metabolites in general had higher plasma free fraction than abemaciclib. Metabolism in liver microsomes and cryopreserved hepatocytes in rats, dogs, and humans indicated formation of 4 oxidative metabolites, including an active (based on *in vitro* binding data) N-desethyl metabolite (LSN2839567). *In vivo* in rats and dogs, parent was detected as the major component in plasma, and formation of the N-desethyl metabolite was observed as the major biotransformation pathway in these species. Excretion studies in rats and dogs indicated that, following oral administration, the majority of the dose was excreted in the bile or feces.

5.3.3. Nonclinical Pharmacokinetic/Pharmacodynamic Modeling

The primary objective of pharmacokinetic/pharmacodynamic modeling in preparation for the Phase 1 study was to estimate a pharmacologically effective and safe dose range in humans, based on preclinical data.

The nonclinical pharmacokinetic/pharmacodynamic analysis of abemaciclib activity for CDK4/6 and tumor growth inhibition (TGI) was conducted on data generated using a Colo-205 xenograft model developed in the mouse. A pharmacokinetic/pharmacodynamic model was developed to relate the predicted plasma concentrations to the observed level of *in vivo* CDK4/6 inhibition and tumor growth inhibition in the Colo-205 xenograft tumor model. Abemaciclib plasma concentrations were connected to CDK4/6 inhibition and cell cycle arrest in Colo-205 human colorectal xenografts by incorporating the biomarkers, pRb, topoIIα, and pHH3, into a precursor-dependent transit compartment model (Sharma et al. 1998; Sun and Jusko 1998; Mager and Jusko 2001; Hazra et al. 2006). This biomarker model was then connected to TGI by i) relating the rate of tumor growth to mitotic cell density, and ii) incorporating a concentration-dependent mixed cytostatic/cytotoxic effect driving quiescence and cell death at high doses. Model validation was evaluated by predicting abemaciclib-mediated antitumor effect in A375 human melanoma xenografts.

The model successfully described abemaciclib-mediated CDK4/6 inhibition, cell cycle arrest, and TGI in Colo-205, and was successfully validated in A375 by effectively predicting CDK4/6, cell cycle, and TGI. The model also demonstrated that a chronic dosing strategy achieving minimum steady state trough plasma concentrations of 200 ng/mL is required to maintain durable cell cycle arrest. High abemaciclib plasma concentrations led to quiescence and apoptosis.

5.3.4. 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 toxicity profile associated with abemaciclib administration in rat and dog was generally

similar to a cytotoxic chemotherapeutic agent, primarily including bone marrow suppression and gastrointestinal toxicity. Clinical signs in animals included fecal changes (soft/liquid, mucoid, discolored – dogs), alopecia and dried/flaking/scabbed skin (rats), vomiting (dogs), decreased food consumption and body weight, dehydration, and decreased activity.

The following paragraphs provide a summary of the major findings in rats and dogs associated with administration of abemaciclib. The repeat-dose 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) and also included a 28-day recovery period to assess reversibility. The dosing schedule corresponds to 1 cycle of dosing in the Phase 1 clinical study. Mortality attributed to abemaciclib was limited to the highest doses investigated, which were 50 mg/kg (300 mg/m^2) in rats and 10 mg/kg (200 mg/m^2) in dogs. In rats, mortality occurred in 2 of 48 rats at 50 mg/kg on Days 14 and 20 and was associated with clinical signs of soft stools and/or reduced feces, dehydration, reduced food consumption, body weight loss, and decreased activity. These mortalities, which were only observed in the toxicokinetic group, were attributed to both administration of abemaciclib and the weakened condition of the animals due to repeated blood sampling.

In dogs, declining clinical condition of animals given 10 mg/kg/day began on Day 9, leading to euthanasia of 2 dogs on Days 12 and 15 and early termination of the dose group on Day 16. The dogs that were euthanized exhibited clinical signs including but not limited to: red and/or liquid and/or soft feces, decreased activity and food consumption, body weight loss, dehydration, thinness, hypothermia, and paleness. These animals also exhibited marked pancytopenia characterized by decreases in reticulocytes, leukocytes (neutrophils, monocytes, and lymphocytes), and platelets. The cause of the mortality in dogs was attributed to gastrointestinal lesions in conjunction with marked myelosuppression. A complete battery of safety pharmacology evaluations was also conducted.

The primary target organs in rats and dogs were identified as bone marrow, gastrointestinal tract, lymphoid tissues, and male reproductive tract. Morphologic changes in these organs were consistent with cytotoxic effects in rapidly dividing cells. Pancytopenia in the peripheral blood and bone marrow hypocellularity were observed at all doses, while effects on the gastrointestinal (crypt hyperplasia and villous atrophy) and lymphoid (depletion in the thymic cortex and lymph nodes) tissues mainly occurred at higher doses. Cytotoxic effects on the male reproductive tract (hypospermatogenesis and atrophy of the testicular seminiferous epithelium, seminal vesicle, and prostate) were also observed in rats and dogs. All of these changes demonstrated complete or partial reversibility within the 28-day recovery period. In an embryo-fetal development study in which pregnant rats received abemaciclib, increased rates of skeletal and cardiac variations and malformations were observed at 4 mg/kg and above. This increased rate of variations and malformations was accompanied by decreased fetal weights. Based on embryo-fetal development studies, there is a risk of fetal toxicity, including teratogenicity, at clinically relevant exposure levels if a pregnant woman is exposed to abemaciclib.

In rats, the lung was also identified as a target organ for toxicity, characterized by multifocal

macrophage accumulation with or without bronchoalveolar inflammation. Minimal-to-slight macrophage accumulation was observed at all doses, whereas minimal-to-moderate inflammation was seen at higher doses. The inflammatory infiltrates were located primarily in the alveoli and composed of mixed cells (neutrophils, macrophages, lymphocytes); hyperplasia of the lining pneumocytes and/or fibrosis was sometimes associated with the inflammation. These changes could be compatible with infection. The inflammation demonstrated complete reversibility within the 28-day recovery period.

Other morphologic changes seen in either rats or dogs were generally considered minor and not considered to be toxicologically important. In rats, microscopic changes at higher doses included minimal-to-slight tubular vacuolar degeneration in the kidneys (without any evidence of renal functional impairment); minimal-to-slight diffuse vacuolation of acinar cells in the pancreas (without any evidence of cellular degeneration or functional impairment); minimal macrophage vacuolation in the spleen; a minor increased incidence of myofiber degeneration/necrosis; and minimal-to-slight hypercellularity of the thymic medulla. In dogs, minimal-to-moderate cytoplasmic eosinophilia/decreased vacuolation and minimal-to-slight mononuclear cell infiltration were seen in the adrenal gland, which were not accompanied by a notable change in cell size or evidence of degeneration.

Abemaciclib was also investigated in a standard battery of safety pharmacology and genotoxicity studies. No adverse findings associated with respiratory or CNS function were observed in rats at up to 50 mg/kg. abemaciclib was negative in the bacterial mutation test (Ames) and *in vitro* and *in vivo* mammalian tests (chromosome aberration and rat micronucleus, respectively), and is thus not considered to be a genotoxicant.

In the cardiovascular safety pharmacology study, dogs were given abemaciclib at doses of 0.3, 1.0, and 10 mg/kg (6, 20, and 200 mg/m^2). Ventricular premature complexes (VPCs) and paroxysmal ventricular tachycardia (VT) occurred in 1 of 8 dogs given 10 mg/kg, a dose that exceeded the MTD in the 28-day repeat-dose toxicity study. Although occasional VPC can be a normal variant in dogs, paroxysmal VT is not a normal finding. These arrhythmias were observed at several time points between 22 and 48 hours postdose. Although parent drug is detectable during this period, the occurrence of VT did not correlate with maximum plasma level of abemaciclib. No waveform abnormalities or blood pressure changes were associated with this arrhythmia. Based upon the incidence in a single animal and the delayed onset, the VT was likely due to ventricular irritation originating from the insertion site of the left ventricular pressure transducer and/or positive electrocardiogram electrode. However, because the arrhythmia occurred only at the highest dose of abemaciclib, it cannot be ruled out as a potential compound-related effect.

In *in vitro* studies, abemaciclib did not demonstrate blockade of the current produced by the human ether-á-go-go-related gene potassium channel expressed in mammalian cells. However, the 50% inhibition concentration (IC_{50}) was not precisely determined due to incompatibility of the compound with the buffer system used in the assay; hence, the IC_{50} was determined to be >1.65 μM. Importantly, no corrected QT interval (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

to be low.

Abemaciclib was also evaluated *in vitro* for ocular irritation using the bovine corneal opacity and permeability test. Based on the results, abemaciclib is considered to be a nonirritant.

Based on the light absorbing properties of abemaciclib and its distribution to the eye and skin in rats, there is the potential for phototoxicity if patients are exposed to sunlight or other sources of ultraviolet light. Specific studies in animals or humans exposed to ultraviolet light have not been conducted yet; while taking abemaciclib, subjects should be advised to avoid the use of tanning beds and, if long exposure to sunlight is expected, to use sunscreen and wear sunglasses.

In conclusion, results from the nonclinical toxicology, safety pharmacology, and genetic toxicology studies for abemaciclib demonstrate an acceptable safety profile with toxicities that are generally considered to be monitorable and reversible. Based on the safety profile of abemaciclib in 28-day toxicology studies, dose/exposure multiples relative to relevant clinical dose levels based on body surface area and mean plasma exposure obtained from patients in Study JPBA are summarized in (Table JPBR.5.1). Although the exposure multiples in animals relative to the clinical doses are low, the toxicology findings associated with abemaciclib in animals and humans are considered to be easily monitorable and have been demonstrated to be reversible. Therefore, collectively, the nonclinical toxicology studies support clinical investigation of abemaciclib.

Table JPBR.5.1. Exposure Multiples for Oral Administration of Abemaciclib Based on Administered Dose in Animals and Human Exposure in Study JPBA

	Dose per day (mg/kg)	Dose per day (mg/m^2)	Dose Multiple[a]	$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	Exposure Multiple[b]
Human[c]					
150 mg Q12H (300 mg per day)	5	187.5	Rat: 1.6 Dog: 0.3	3,758[d]	Rat: 6.5 Dog: 0.2
200 mg Q12H (400 mg per day)	6.7	250	Rat: 1.2 Dog: 0.2	5,886[d]	Rat: 4.3 Dog: 0.1
Rat NSTD[e]	50	300	-	23,800	-
Dog MinTD[f]	3	60	-	800	-

Abbreviations: AUC0-24 hr = area under the concentration versus time curve from time 0-24 hours; MinTD = highest Minimally Toxic Dose; NSTD = highest Not Severely Toxic Dose; Q12H = every 12 hours.

a Dose multiple is the dose in animals/dose in humans based on body surface area (mg/m2).

b Exposure multiple is the mean calculated AUC0-24 hr (males and females) on Day 1 in animals/AUC0-24 hr in humans at steady state.

c Assumes body weight of 60 kg and body surface area of 1.6 m2.

d Human exposure (steady state) derived from clinical pharmacokinetic data collected in Study JPBA.

e NSTD based on 28-day repeat-dose toxicity study in rats (803871).

f MinTD based on 28-day repeat-dose toxicity study in dogs (803872).

More detailed information about the characteristics of abemaciclib can be found in the IB.

5.3.5. Biomarkers

Not applicable.

5.3.6. Clinical Experience

As of 22 September 2016, 12 clinical studies were completed (7 in healthy subjects and 5 in patients) and 19 clinical studies are ongoing (3 in healthy subjects and 16 in patients). Among them, Study JPBA was a multicenter, nonrandomized, open-label Phase 1 study of abemaciclib in patients with advanced and/or metastatic cancers. In Part A (the dose-escalation phase), patients were treated on 2 different schedules: either at 50, 100, 150, and 225 mg every 24 hours (Q24H), or at 75, 100, 150, 200, and 275 mg every 12 hours (Q12H). In Parts B, C, D, E, F, and G (the tumor-specific cohorts), patients were treated on the twice-daily schedule at a dose no greater than the MTD with administration of abemaciclib on Days 1 through 28 of a 28-day cycle. The MTD was not reached for the once-daily schedule and for the twice-daily schedule was established at 200 mg Q12H. The Phase 2 study, JPBB, is a proof-of-concept trial for patients with mantle cell lymphoma (MCL). Abemaciclib is administered orally at 200 mg Q12H on Days 1 through 28 of a 28-day cycle. Study JPBC, was a dose acceleration Phase 1 trial in

Japanese patients with advanced and/or metastatic cancers designed to confirm the safety and tolerability of abemaciclib up to the MTD which was established in Study JPBA. Study I3Y-MC-JPBD (JPBD) is an open-label study to determine the disposition of labeled abemaciclib in healthy surgically sterile or postmenopausal females or sterile males following oral administration of a single 150-mg dose of abemaciclib containing approximately 5 μCi of [^{14}C]-abemaciclib. A food-effect study (I3Y-MC-JPBG [JPBG]) involving administration of abemaciclib as a 50% w/w capsule to healthy volunteers with a high-fat meal indicated that the Cmax was increased 24% while the AUC remained unchanged, when compared to the fasted state. Results from a study (I3Y-MC-JPBU [JPBU]) of the effect of a high-fat meal using the proposed commercial formulation (25% w/w capsule) show an increase of approximately 30% in AUC and C_{max} in the presence of food. A high-fat meal did not change the interindividual variability in PK. Although the change in AUC and C_{max} in Study JPBU was statistically significant, it was small relative to the variability in exposure in the cancer patient population, and therefore not considered to be clinically relevant. Based on currently available data, abemaciclib can be taken without regard to meals.

5.3.6.1. Clinical Pharmacokinetics

The PK profile of abemaciclib was studied using data available from a total of 222 patients enrolled in Study JPBA.

A nonclinical PK/PD model has demonstrated that a chronic dosing strategy achieving minimum steady state trough plasma concentrations of 200 ng/mL is required to maintain durable cell cycle arrest.

Clinically, after a single oral dose administration, the time course of abemaciclib in plasma at the MTD of 200 mg is characterized by a median T_{max} of 6 hours (cancer patients) and a mean $t_{1/2}$ of approximately 21.3 hours. The mean C_{max} and $AUC_{0\text{-tlast}}$ are 158 ng/mL and 4600 ng*hr/mL, respectively.

At steady state after repeated oral Q12H dosing, the time course of abemaciclib concentration in plasma at the MTD is characterized by a mean $C_{min,ss}$ and $C_{max,ss}$ of approximately 197 and 298 ng/mL, respectively. The mean $AUC_{0\text{-}\tau,ss}$ and $AUC_{0\text{-}24,ss}$ are approximately 3000 and 5520 ng.hr/mL, respectively.

5.3.6.2. Safety

As of 22 September 2016, abemaciclib has been administered to 2087 cancer patients. There are 16 ongoing and 5 completed clinical studies in cancer patients. Clinical study data are available for 870 patients from 5 completed studies (JPBA, JPBB, JPBC, JPBE, and JPBN and 3 ongoing studies (JPBH, JPBJ, and JPBY). LSS data are available from Studies JPBA, JPBB, JPBC, JPBE, JPBH, JPBJ, JPBK, JPBN, JPBO, JPBZ, JPBX, JPBY, and JPCB.

Overall, the most common TEAEs (≥10%) possibly related to study drug for patients receiving abemaciclib as a single agent are diarrhea, nausea, fatigue, neutropenia, vomiting, decreased appetite, thrombocytopenia, anemia, leukopenia, abdominal pain, and blood creatinine increased.

In Study JPBH, when abemaciclib was combined with endocrine therapy (anastrozole, letrozole,

tamoxifen, exemestane), diarrhea has been reported in 98.5% of the metastatic breast cancer patients; and in 86.0% of the metastatic breast cancer patients when combined with targeted agents (exemestane + everolimus, or trastuzumab). As a result of the higher incidence of diarrhea, the recommended abemaciclib dose is 150 mg Q12H when combined with these agents. Furthermore, it was noted in Study JPBY (abemaciclib 150 mg Q12H in combination with anastrozole), diarrhea was reduced at 52% when patients received loperamide prophylactically.

The majority of deaths reported for patients in the presented studies with available safety data were due to disease progression.

Per LSS as of 22 September 2016, 167 patients in the ongoing and completed cancer patient studies experienced 264 SAEs that were reported as possibly related to study drug. SAEs that were possibly related to study drug and experienced by ≥5 patients receiving abemaciclib monotherapy included diarrhea (14 patients); nausea (9 patients); acute kidney injury and dehydration (7 patients each); anemia, pneumonia, and vomiting (6 patients each); and neutropenia and thrombocytopenia (5 patients each).

Two, unexpected hepatic SAEs (1 of liver failure and 1 of drug-induced liver injury) were identified in the open-label Phase 3 JUNIPER (I3Y-MC-JPBK) study comparing abemaciclib versus erlotinib in patients with Stage IV NSCLC. Both of these hepatic SAEs had confounding factors including prior treatment with nivolumab and baseline hepatic metastases.

SAEs that were possibly related to study drug and experienced by ≥5 patients receiving abemaciclib combinations included neutropenia (5 patients; abemaciclib with pemetrexed) and dehydration (5 patients; abemaciclib with endocrine therapy).

5.4. Rationale for Selection of Dose

During dose escalation part in Study JPBA, the dosages of 50, 100, 150, and 225 mg every 24 hours (Q24H), and 75, 100, 150, 200, and 275 mg Q12H were investigated. None of the patients treated on the once-daily schedule and 3 of the 33 patients (9.1%) treated on the twice-daily schedule experienced dose-limiting toxicities (DLTs). At 275 mg Q12H, 2 of the 3 patients experienced DLTs of Grade 3 fatigue (1 of these patients also experienced a DLT-equivalent event of Grade 3 nausea on Day 6 of Cycle 2). At the next lower dose level of 200 mg Q12H, 1 of the 7 patients also experienced a DLT of Grade 3 fatigue. Therefore, the MTD was established at 200 mg Q12H. Thus, a global multicenter, open-label, randomized Phase 3 trial, I3Y-MC-JPBK, is planned to compare the efficacy and safety of abemaciclib 200 mg orally administrated every 12 hours versus erlotinib treatment for patients with Stage IV NSCLC whose tumors have a detectable KRAS mutation and who have progressed after platinum-based chemotherapy. Patients from China will be enrolled in this global Phase 3 study.

Preliminary safety data from Study JPBH, which is a Phase 1b study to evaluate safety and tolerability of abemaciclib in combination with endocrine therapies (including anastrozole and letrozole) in patients with advanced/metastastic breast cancer, demonstrates that the AE profile of 150-mg or 200-mg Q12H abemaciclib administered in combination with NSAIs is consistent with abemaciclib monotherapy, as the most common TEAEs possibly related to study drug were

diarrhea, nausea, fatigue, and neutrophil count decreased. At the 200-mg dose, the incidence of treatment-emergent Grade 3 diarrhea was found to be greater when abemaciclib was administered in combination with an NSAI from a review of the preliminary safety data in Study JPBH, compared to abemaciclib administered alone in Part D of Study JPBA. When the abemaciclib dose was reduced from 200 mg to 150 mg or lower for some patients in Study JPBH, either the severity of diarrhea decreased or the event resolved. Therefore, a multicenter, randomized Phase 3 study, Study JPBQ, is planned to compare the efficacy and safety to compare NSAI plus 150-mg abemaciclib or plus placebo, and to compare fulvestrant plus 150-mg abemaciclib or plus placebo in mainly east Asian postmenopausal women with hormone receptor-positive, HER2-negative, locoregionally recurrent or metastatic breast cancer.

Since the objective of Study JPBR is to evaluate the safety and tolerability of abemaciclib monotherapy in Chinese patients with advanced and/or metastatic cancers and to support the subsequent Phase 3 studies in NSCLC and metastatic breast cancer (Studies JPBK and JPBQ) to be conducted in China, both doses of 150 mg and 200 mg Q12H will be evaluated in the study.

6. Investigational Plan

6.1. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may, in principle, not be re-screened. Individuals who previously failed screening due to minor abnormalities of clinical laboratory tests, may be re-tested by agreement between principal investigator and the sponsor.

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 first dose of study drug.

[1] The patient must have histological or cytological evidence of cancer which is advanced and/or metastatic, and is an appropriate candidate for experimental therapy in the judgment of the investigator, after available standard therapies have ceased to provide clinical benefit.
[2] Have the presence of measureable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1, Eisenhauer et al. 2009).
[3] This criterion has been deleted.
[4] This criterion has been deleted.
[5] This criterion has been deleted.
[6] Are native Chinese men or women≥18 years of age.
[7] Have given written informed consent prior to any study-specific procedures.
[8] Have adequate organ function, including:

- Hematologic: Absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, and hemoglobin≥9 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level or receive platelet transfusion at the discretion of the investigator; however, initial study drug treatment must not begin earlier than the day after transfusion.
- Hepatic: Bilirubin ≤1.5 times upper limits of normal (ULN), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3.0 times ULN.
- Renal: Serum creatinine ≤1.2 mg/dL for males or ≤1.0 mg/dL for females.

[9] Have a performance status ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al. 1982).
[10] Recovered from the acute effects of therapy (treatment-related toxicity resolved to baseline) except for residual alopecia.
[11] Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.
[12] Males and females with reproductive potential must agree to use medically approved precautions to avoid pregnancy during the trial and for 3 months following the last dose of study drug.

[12a] Are a man and agree to use a reliable method of birth control and to not donate sperm during the study and for at least 3 months following the last dose of study drug, OR

[12b] Are a woman of child-bearing potential with a negative serum pregnancy test at baseline (within 7 days prior to randomization) and agree to use a reliable method of birth control during the study and for 3 months following the last dose of the study drug.
A woman of child-bearing potential is defined as a premenopausal female. A postmenopausal female is defined as a woman:
1) at least 6 weeks after surgical bilateral oophorectomy that can be confirmed on medical history records, OR
2) with spontaneous amenorrhea for at least 12 months, not induced by a medical conditions such as anorexia nervosa nor induced by medication.

[13] Have an estimated life expectancy of ≥12 weeks.
[14] Are able to swallow capsules.

6.1.2. Exclusion Criteria

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

[15] Have received previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and investigational therapy) within 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents prior to receiving study drug.
[16] Have a personal history of any of the following conditions: presyncope or syncope of either unexplained or cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest, or have a baseline ECG with any of the following abnormal findings: ventricular arrhythmia, evidence of acute myocardial ischemia, heart block (of any degree), or QTc prolongation (defined as QTcB ≥450 milliseconds).
[17] Have serious 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).
[18] Have an acute leukemia or other relevant cancers at the discretion of the investigator.
[19] Females who are pregnant or lactating.
[20] Have active bacterial, fungal, and/or known viral infection (for example, human immunodeficiency virus [HIV] antibodies, hepatitis B surface antigen [HBSAg], or hepatitis C antibodies). Screening for active infections is not required for enrollment.
[21] Patients consuming drugs or foods that are known to be inducers (for example, grapefruit juice, phenytoin, carbamazepine) or strong inhibitors of CYP3A4 should be excluded during Cycle 1 (Attachment 6).
[22] Patients receiving herbal regimens during Cycle 1 should be excluded.

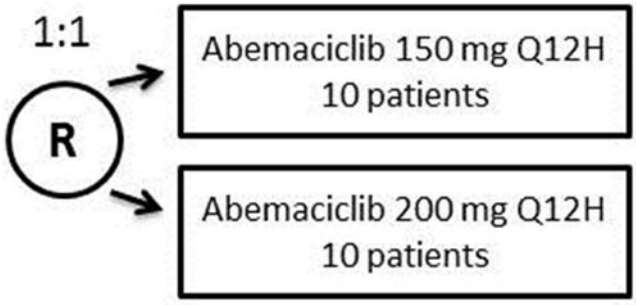
[23] Have history or evidence of CNS malignancy or metastasis. Screening of asymptomatic patients without history of CNS metastases is not required for enrollment.
[24] This criterion has been deleted.

6.2. Summary of Study Design

This study is a multicenter, open-label, Phase 1 trial of abemaciclib in Chinese patients with advanced and/or metastatic cancers.

The study will be focused on safety evaluation and PK data collection in patients with all advanced and/or metastatic cancers. Patients will be randomized into 2 dose cohorts, and orally receive abemaciclib 150 mg or 200 mg every 12 hours (Q12H). One cycle is defined as 28 days (Cycle 1: 32 days), with modifications during Cycle 1 to enable PK sampling following a single dose and repeated doses. The treatment of abemaciclib will continue until disease progression, development of unacceptable toxicity, or fulfillment of the other discontinuation criteria. In case of patient discontinuation during Cycle 1, the enrollment will be extended until at least 10 patients with completed PK data accrued in each cohort. Analysis on available PK and safety data will be conducted after study completion.

All patients in the study receive at least 2 cycles of abemaciclib unless one or more of the criteria for discontinuation (refer to Section 6.3.1) are fulfilled; the short-term follow-up period for poststudy evaluation is 30 ±7 days after the decision to discontinue treatment. Figure JPBR.6.1 shows the study design for Study JPBR.



Abbreviations: Q12H = every 12 hours; R = randomization.

Figure JPBR.6.1. Study design for JPBR.

Refer to Attachment 1 for the Study Schedule.

6.2.1. Study Completion and End of Trial

6.2.1.1. Study Period

Study period begins at the first study treatment and ends at study completion. The study period does not include the continued access period. **Study completion** will occur after all patients have been in study treatment for at least 6 cycles, or after all patients have discontinued study treatment and completed the short-term follow-up visit, whichever occurs earlier. Refer to

Attachment 2 for the Study Schedule for the continued access period.

Short-term follow-up will begin the day after the patient and the investigator agree to discontinue abemaciclib and lasts approximately 30 (±7) days.

Long-term follow-up will begin the day after short-term follow-up is completed and continues to study completion.

6.2.1.2. Continued Access Period

Continued access begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit may continue to receive study treatment until one of the criteria for discontinuation is met. Lilly will notify investigators when the continued access period begins. Approximate visit duration of continued access is 28±2 days. Continued access follow-up will begin the day after the patient and the investigator agree to discontinue abemaciclib and lasts approximately 30 (±7) days. All AE and SAE information will be collected in continued access. Efficacious measurement will be at the discretion of the investigator.

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

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

6.2.1.3. End of Trial

End of trial is 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 the final follow-up visit (including the final follow-up visit for the continued access period, if applicable) or has been declared lost to follow-up.

6.3. Discontinuation

6.3.1. Discontinuation of Patients

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 clinical research physician (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.

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 drugs
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drugs 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 good clinical practice (GCP)
- The patient has evidence of progressive disease.
- The patient experiences unacceptable toxicity, including but not limited to the following circumstance (refer to Section 7.2.3.1.2.2).
- Patients not recovering from toxicity within 14 days should be considered for discontinuation of the study. A delay >14 days may be permitted before discontinuing the patient from treatment as long as the patient demonstrates clinical benefit without objective progression and is recovering from the toxicity. Such a decision should be discussed and documented with the Lilly CRP.

The patient is noncompliant with study procedures and/or treatment (Section 7.6).

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 CRF. Patients who discontinue will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

6.3.2. 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.

6.3.3. Discontinuation of the Study

The study will be discontinued if Lilly, while considering the rights, safety, and well-being of the patients, judges it 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 will be supplied as capsules for oral consumption. Abemaciclib capsules should be stored within the temperature range stated on the label. Investigators should instruct patients to store the capsules at home in the original container and to keep out of the reach of children. Capsules should not be opened, crushed, or dissolved.

Clinical study materials will be labeled according to the country's regulatory requirements.

7.2. Study Drug Administration

The investigator or designee is responsible for:

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

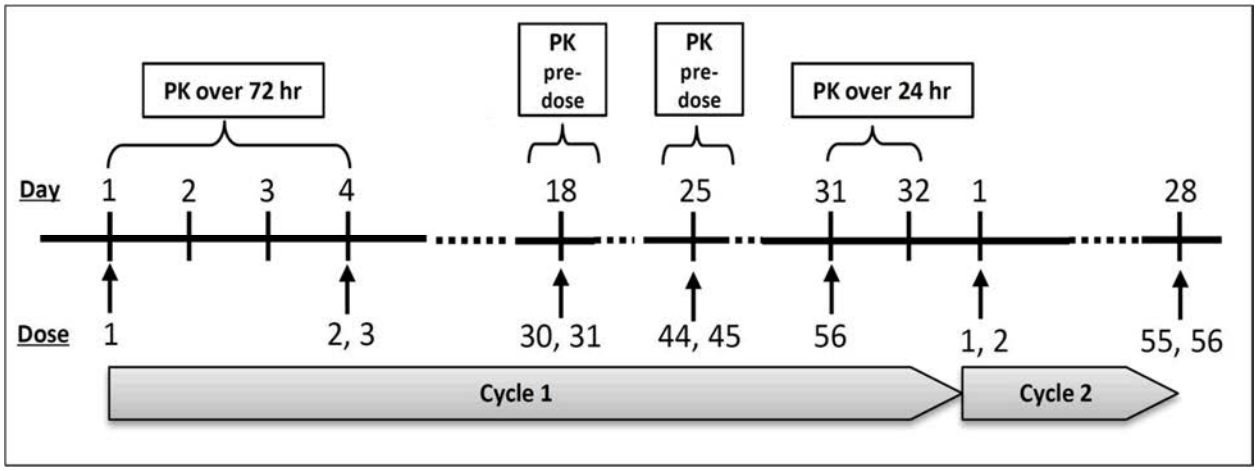
Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

7.2.1. Dosing Schedule

Oral abemaciclib will be administered every 12 hours (±3 hours) on 28-day cycles (Cycle 1: 32 days). Study drug should be taken at approximately the same times each day.

For Cycle 1, the initial dose of study drug will be taken on Day 1 to enable PK sampling over 72 hours following a single dose; the remaining 55 doses will be taken every 12 hours on Days 4 to 31, with additional PK sampling on Day 18, Day 25, and over 24 hours following the single dose taken on Day 31 as scheduled in Attachment 5. For Cycle 1, patients should be specifically instructed not to take a second dose of study drug on Day 31; if such a dose is inadvertently taken on Day 31, it constitutes a protocol violation. In principle, patients will be suggested to be hospitalized during PK sample collection especially for Day 1 and Day 31 in Cycle 1.

Figure JPBR.7.1 shows the PK sampling and dosing schedule for Study JPBR.



Abbreviation: PK = pharmacokinetic(s).

Figure JPBR.7.1. PK sampling and dosing schedule.

From Cycle 2, patients will be administrated every 12 hours on Days 1 through 28 of a 28-day cycle.

A delay of ≤7 days in the initiation of a cycle (Day 1) for justifiable reasons (for example, inclement weather, holidays, or weekends) other than toxicity will be permitted. Study treatment may be held up to 14 days within a cycle or at start of next cycle to permit sufficient time for recovery from the toxicity.

Patients will receive at least 2 cycles of abemaciclib unless one or more of the criteria for discontinuation (refer to Section 6.3.1) are fulfilled; the short-term follow-up period for poststudy evaluation will be 30 ±7 days after the decision to discontinue treatment.

7.2.2. DLT-Equivalent Toxicity

The dose-limiting toxicity (DLT)-equivalent toxicity is defined as an AE occurring between 1) Day 1 and Day 32 of Cycle 1; 2) Day 1 and Day 28 of Cycle 2 and beyond, that is possibly related to the study drug and fulfills any one of the following criterion using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0:

- Grade 3 or 4 nonhematological toxicity according to the NCI CTCAE Version 4.0 except for nausea, vomiting, diarrhea, or electrolyte disturbance.
- Grade 3 or 4 nausea, vomiting, diarrhea, or electrolyte disturbance that persists more than 2 days despite maximal supportive intervention.
- Grade 4 hematological toxicity that persists more than 5 days.
- Grade 3 or 4 thrombocytopenia with bleeding.
- Grade 3 or 4 neutropenia with fever.

7.2.3. Dose Adjustments and Delays

7.2.3.1. Dose Adjustments

Dose adjustments are allowed both within a cycle and between cycles.

If a patient who, in the judgment of the investigator, is receiving clinical benefit from study therapy requires further dose reduction than is outlined in Table JPBR.7.2, then the investigator must discuss with the Lilly CRP prior to any further dose reduction.

Dose adjustments are allowed only one level at a time. For patients requiring dose reduction(s), re-escalation to a prior dose level is permitted only after consultation with the Lilly CRP.

Dose adjustments and delays for the study are summarized in Table JPBR.7.1.

Table JPBR.7.1. Toxicity Dose Adjustments and Delays of Study Drug for Study JPBR

Cause	Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity Section 7.2.3.1.1	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MAY** be reduced by one dose level.
Hematologic Toxicity Section 7.2.3.1.1	Recurrent Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by one dose level.
Hematologic Toxicity Section 7.2.3.1.1	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by one dose level.
Hematologic Toxicity: If **patient requires administration of blood cell growth factors** Section 7.2.3.1.1	Regardless of severity (Use of growth factors according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by one dose level unless already performed for incidence of toxicity that led to the use of growth factor
Nonhematological Toxicity[b] (except diarrhea and ALT increased) Section 7.2.3.1.2	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by one dose level.
Nonhematological Toxicity Section 7.2.3.1.2	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by one dose level.
Diarrhea Section 7.2.3.1.2.1 and 7.5.1	Grade 2 that does not resolve within 24 hours to at least Grade 1	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose reduction is **NOT** required.
Diarrhea Section 7.2.3.1.2.1 and 7.5.1	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures ,or any Grade of diarrhea that requires hospitalization.	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by one dose level.

Diarrhea Section 7.2.3.1.2.1 and 7.5.1	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by one dose level.
ALT Increased (Sections 7.2.3.1.2.2. and 8.1.4.1)	Persistent or recurrent[a] Grade 2 (>3.0-5.0×ULN), or Grade 3 (>5,0-20.0×ULN)[c]	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT Increased (Sections 7.2.3.1.2.2. and 8.1.4.1)	Grade 4 (>20.0×ULN)	Study drug **MUST** be discontinued.	Study drug **MUST** be discontinued.
ALT Increased with increased total bilirubin, in the absence of cholestasis (Sections 7.2.3.1.2.2.)	Grade 3 increased ALT (>5.0 x ULN) with total bilirubin >2 x ULN	Study drug MUST be discontinued	Study drug MUST be discontinued

Abbreviation: ALT = alanine transaminase; ASCO = American Society of Clinical Oncology.
Note: MUST = mandatory.

a Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:
- shows stable hematological counts (Grade ≤2) during that timeframe
- has absence of any signs or risk of infection
- is benefiting from study treatment

b Additional guidance for renal and hepatic monitoring is in Sections 8.1.4.1 and 8.1.4.2.

c Grade 3 ALT increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 8.1.4.1 for additional guidance for hepatic monitoring

7.2.3.1.1. Hematologic Toxicity

If a patient experiences Grade 4 hematologic toxicity, then study treatment must be suspended (until the toxicity resolves to either baseline or at least Grade 2) and the dose of abemaciclib must be reduced by one dose level as outlined in Table JPBR.7.2.

If a patient experiences Grade 3 hematologic toxicity, then study treatment must be suspended (until the toxicity resolves to either baseline or at least Grade 2) and the dose of abemaciclib may be reduced by one dose level as outlined in Table JPBR.7.2 at the discretion of the investigator.

If the patient experiences a recurrent episode of Grade 3 hematologic toxicity, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of the study must be reduced by one dose level as outlined in Table JPBR.7.2.

Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3

hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:

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

If a patient requires administration of blood cell growth factors, the dose of study drug must be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2, then reduced by one dose level as outlined in Table JPBR.7.2, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

7.2.3.1.2. Nonhematological Toxicity

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. 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 JPBR.7.2.

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea; refer to Section 7.2.3.1.2.1 or ALT increased, refer to Section 7.2.3.1.2.2) possibly related to abemaciclib that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, then dosing 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 JPBR.7.2.

7.2.3.1.2.1. 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 either baseline or at least Grade 1) and must have abemaciclib dose reduced by one dose level as outlined in Table JPBR.7.2.

If a patient experiences persistent or recurrent diarrhea (Grade 2) that does not resolve with maximal supportive measures (refer to Section 7.5.1) within 24 hours to either baseline or at least Grade 1, then study treatment must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib must be reduced by one dose level as outlined in Table JPBR.7.2.

Table JPBR.7.2. Dose Adjustments of Abemaciclib for Study I3Y-CR-JPBR

Dose Adjustment	Oral Dose (For patients initiated with 200 mg)	Oral Dose (For patients initiated with 150 mg)	Frequency
0	200 mg	150 mg	Every 12 hours
1	150 mg	100 mg	Every 12 hours
2	100 mg	50 mg	Every 12 hours
3	50 mg	-	Every 12 hours

7.2.3.1.2.2. Hepatic Toxicity

Dose modifications and management for increased ALT are provided in Table JPBR.7.1. For persistent or recurrent Grade 2 ALT increased that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1, or Grade 3 ALT increased, blinded study drug must be suspended until the toxicity has resolved to at least Grade 1 and the dose must be reduced by 1 dose level. Discontinue blinded study drug for Grade 3 increased ALT (>5.0 x ULN) with total bilirubin >2 x ULN, in the absence of cholestasis. For Grade 4 ALT increased, the patient must be discontinued from blinded study drug. Refer to Section 8.1.4.1 for additional hepatic monitoring guidance.

7.2.3.2. Dose Delays

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

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

The start of a cycle may be delayed to allow sufficient time for recovery from toxicity possibly related to study drug. Patients not recovering from such toxicity within 14 days should be considered for discontinuation from the study.

7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive abemaciclib in this study. Before each patient's enrollment into the study, an eligibility check must be conducted at the investigational site to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose and identification number assignment for each patient using the interactive web response system (IWRS).

Upon obtaining informed consent, site personnel should access the IWRS, which will enter a patient number. Patients who meet all criteria for enrollment will be randomly assigned to receive either 150-mg or 200-mg abemaciclib. A simple randomization method will be adopted. Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS. Site personnel will confirm that they have located the correct dosage by entering a confirmation number found on the packages into the IWRS.

7.4. Blinding

This is an open-label study.

7.5. Concomitant Therapy

No other chemotherapy, immunotherapy, or experimental medications will be permitted while the patients are on this study. Due to the Phase 1 PK testing and possible unknown interactions, all herbal supplements will not be allowed while patients in Cycle 1, herbal therapies for cancer will not be permitted while patients are in Cycle 2 and beyond Cycle 2. Palliative radiotherapy on a painful bone lesion, unless required due to progressive disease, is permitted during the study. 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 for each cycle on the electronic case report form (eCRF). Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day short-term follow-up visit.

The results from an *in vitro* human recombinant cytochrome P450 (CYP) phenotyping study indicate that oxidative metabolism of abemaciclib is primarily catalyzed by CYP3A4. Radiolabeled human disposition study indicates that abemaciclib is mostly cleared by oxidative metabolism. Based on these findings, grapefruit juice as well as inducers (for example, phenytoin, carbamazepine) and strong inhibitors of CYP3A4 should be excluded during PK phase (Cycle 1) of the study treatment, and should be avoided during other cycles of study treatment period (Attachment 6).

In addition, *in vitro* studies in primary cultures of human hepatocytes indicate that abemaciclib and its major metabolites LSN2839567 (M2) and LSN3106726 (M20) down regulate mRNA of 1 or more CYPs, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A at clinically relevant concentrations. The mechanism of down regulation and its clinical relevance are presently not understood. Therefore, caution should be exercised when coadministering substrate drugs of the above CYPs with narrow therapeutic margin (Attachment 7).

Patients should receive full supportive care during the trial. Transfusion is permitted at the discretion of the investigator.

Granulopoietic factor (G-CSF) may be used in accordance with ASCO guidelines (Smith et al. 2015) and if they adhere to the dosage and administration described in the China Package Insert.

7.5.1. Supportive Management for Diarrhea

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

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (for example, loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear

liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with antidiarrheal therapy within 24 hours to either baseline or Grade 1, abemaciclib should be suspended until diarrhea is resolved to baseline or Grade 1.
- When abemaciclib recommences, dosing should be adjusted as outlined in Section 7.2.3.1 and Table JPBR.7.2.

In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring 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 intravenous fluid (IV hydration) and electrolyte replacement.

7.6. Treatment Compliance

Patient compliance with study medication will be assessed at each visit by review of the patient diary, direct questioning, and counting of returned capsules. Deviation(s) from the prescribed dosage regimen should be recorded on the CRF.

The patient must take ≥75% of the planned doses in a cycle to be deemed compliant with study drug administration. Similarly, a patient may be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than 125% of the prescribed amount of medication. Any missed doses during a cycle 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 before making the final determination for discontinuation. If a patient is discontinued due to study drug noncompliance, the patient may be replaced.

8. Safety, Pharmacokinetic, 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.

Study procedures and their timing, including tolerance limits for timing, are described in the Study Schedule (Attachment 1).

Blood samples, and ECGs will be collected at the times specified in the Study Schedule (Attachment 1). Laboratory tests including hematology and chemistry will be performed. A serum pregnancy test will be administered to females with child-bearing potential. Attachment 3 lists the specific laboratory tests that will be performed for this study. Enrollment and treatment decisions may be based upon results of tests performed.

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

All concomitant medications should be recorded throughout the patient's participation in the study, until conclusion of the study follow-up period.

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 adverse event and serious adverse event 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 JPBR.8.1 presents a summary of AE and SAE reporting guidelines. Refer to Attachment 8 for specific recommendations about reporting SAEs.

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. All AEs observed will be graded using CTCAE v4.0.

The National Cancer Institute (NCI)-CTCAE v4.0 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 4.0X) 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 NCI-CTCAE v4.0 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 (MedDRA) 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 CRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

The investigator will record all relevant AE/SAE information in the CRF. Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, study drug via CRF.

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 therapy or other protocol-required procedure) should not be considered SAEs.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. An SAE is any adverse event 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

During screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected after the patient has signed the informed consent form (ICF).

8.1.2.2.2. On Therapy

All AEs and SAEs, regardless of relatedness to study drug, 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 drugs or protocol procedures, occurring during the follow-up visit must be reported to Lilly or its designee. The short-term follow-up visit starts following the discontinuation treatment. At the end of the short-term follow-up visit, the patient will be required to have specific safety assessments (Attachment 1). The timing of these safety assessments is 30 ± 7 days after the decision to stop study treatment.

Following the safety assessments, which mark the end of the short-term follow-up visit, the patient will enter the long-term follow-up visit period, 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 anti-cancer treatment prior to the scheduled end of the short-term follow-up visit, the follow-up visit duration may be shortened. In this case, the short-term follow-up assessments should be completed prior to the initiation of the new therapy.

After the short-term follow-up visit, ongoing AEs possibly related to study drug should continue to be followed. If an investigator becomes aware of an SAE 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 (DCSI) 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 AE/SAE Reporting Guidelines

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

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

Period	Types of AEs/SAEs to be Reported	Collection Database	Lilly Safety System
Baseline (pretreatment)	Preexisting conditions All AEs All SAEs regardless of relatedness	x x x	 x
Study treatment period	All AEs All SAEs regardless of relatedness	x x	 x
30-day short-term follow-up	All AEs All SAEs regardless of relatedness	x x	 x
Long-term follow-up	All SAEs related to protocol procedures or study drug	x	x
Continued access period	All AEs All SAEs regardless of relatedness	x x	 x
Continued access follow-up	All AEs All SAEs regardless of relatedness	x x	 x
After the patient is no longer participating in the study (that is, no longer receiving study therapy and no longer in follow-up)	All SAEs related to protocol procedures or study drug that the investigator becomes aware of		x

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

8.1.3. Other Safety Measures

8.1.3.1. Electrocardiograms

During Cycle 1, a 12-lead digital ECG will be collected according to the Study Schedule (Attachment 1) and PK sampling and ECG Schedule (Attachment 5). ECG test schedule will include:

- Day 1: pre-dosing test, 4 and 6 hours post-dosing test

- Day 31: pre-dosing test, 4 and 6 hours post-dosing test

On Day 28(±2) of Cycle 2 and beyond, ECG test will be conducted according to the Study Schedule (Attachment 1).

Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs 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.

ECGs 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 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 from at least 1 of the replicate ECGs from each time point.

8.1.4. Safety Monitoring

The Lilly CRP or 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,
- adverse events,

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C calculated glomerular filtration rate. Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function. See Attachment 3. Dose alterations (omission, reduction and discontinuation) should not solely be based on interpretations of serum creatinine values because they may not reflect renal function.**Special Hepatic Safety Data Collection**

If a study patient experiences elevated ALT ≥5×ULN and elevated total bilirubin (TBL)≥2×ULN,

or ALT >8x ULN for patients with underlying baseline hepatic metastases, liver tests (Attachment 4), including ALT, AST, TBL, direct bilirubin, gamma glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests (Attachment 4) and in consultation with the Lilly CRP. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels. Additional diagnostic testing should be considered to rule out cause of increased liver enzymes per the investigator's discretion.

Hepatic monitoring tests (Attachment 4) should be collected in the event that 1 or more of the following conditions is met for the patient during the course of the study:

- ALT ≥5×ULN and TBL ≥2×ULN
- ALT>8x ULN for patients with underlying hepatic metastasis
- discontinuation from study treatment due to a hepatic event or an abnormality of liver tests

8.1.4.2. Renal Function

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

Dose adjustment (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for non-hematological toxicities (Table JPBR.7.1).

8.1.4.3. Venous Thromboembolic Events

In the randomized Phase 3 studies in breast cancer patients who received abemaciclib in combination with endocrine therapy, there was a greater number of patients who experienced VTEs in the abemaciclib plus endocrine therapy arm than in the placebo plus endocrine therapy arm. The majority of the events were non-serious and were treated with low-molecular-weight heparin. Generally, these events did not result in discontinuation of the study treatment. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. For suspected or confirmed VTE (eg. deep vein thrombosis or pulmonary embolism), treatment should occur according to usual clinical practice.

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

Attachment 4 lists the hepatic monitoring tests that will be performed for this study.

Attachment 5 lists the schedule for PK sample collections and ECGs in this study.

The information of sample disposal methods and blood volumes will be provided as other documents such as ICF.

8.2.1. Samples for Study Qualification and Health Monitoring

Blood 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 Measurements Pharmacokinetics

8.2.2.1. Pharmacokinetic Samples

PK samples will be collected as specified in the Study Schedule (Attachment 1) and the PK Sampling and ECG Schedule (Attachment 5).Venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of abemaciclib and 2 major metabolites (LSN2839567 [M2], and LSN3106726 [M20]). Instructions for the collection and handling of

blood samples will be provided by the sponsor.

These samples will be analyzed at a laboratory designated by the sponsor. Plasma concentrations of abemaciclib and its major metabolites, LSN2839567 (M2) and LSN3106726 (M20), will be determined using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

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

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

Bioanalytical samples collected to measure investigational product concentration and metabolism and/or protein binding, will be retained for a maximum of 1 year following last patient visit for the study.

8.2.3. Biomarker Samples for Storage and Research

Not applicable.

8.3. Efficacy Evaluations

A secondary objective of the study is to document any antitumor activity. Refer to Attachment 1 for details regarding the timing of specific efficacy measures.

Each patient will be assessed by one or more of the following radiologic tests for tumor measurement:

- Computed tomography (CT) scan
- Magnetic resonance imaging (MRI)

Each patient's full extent of disease will also be assessed with:

- Tumor measurement by RECIST 1.1 (Attachment 10, Eisenhauer et al. 2009),
- Evaluation of tumor markers, if indicated,
- Evaluation of performance status (Attachment 9, Oken et al. 1982).

To confirm objective responses, all lesions should be radiologically assessed, and the same radiologic method used for the initial response determination should be repeated at least 4 weeks following the initial observation of an objective response. If a patient is discontinued from the study, repeat radiology assessments may be omitted if clear clinical signs of progressive disease are present.

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 or lab requisition form.

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 eCRFs, 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 eCRF 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 institutional review board (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.

For data handled by the sponsor internally, eCRF 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 laboratory's database system. Data will subsequently be transferred from the central vendor to the Lilly Clinical Laboratory Results Modernization (CLRM) and third-party organization (TPO)'s system.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly CLRM and/or TPO's system.

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

10. Data Analyses

10.1. General Considerations

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

The interpretation of the study results will be the responsibility of the investigator with the Lilly CRP or CRS, pharmacokineticist, and statistician. The CRP or CRS 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.

Safety analyses and all efficacy analyses will be conducted using the full analysis set (FAS), which will include the data from all patients who received at least one dose of any study drug.

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

Detailed information regarding the planned statistical analyses will be described in the Statistical Analysis Plan (SAP).

10.2. Determination of Sample Size

There are no formal sample size calculations. Twenty or more patients may be enrolled to ensure 10 completers (that is, obtained the full set of PK samples for appropriate PK evaluation) in each dose cohort.

10.3. 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.

10.4. Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics will be reported
- Baseline disease characteristics
- Prior disease-related therapies.

Other patient characteristics will be summarized as deemed appropriate.

10.5. Safety Analyses

Safety analyses will be conducted on all patients who have received at least one dose of the study drug. Safety analyses will include summaries of the following data:

- DLT-equivalent toxicity rate
- TEAEs including seriousness, severity, and possible relationship to study drug

- dose adjustments
- laboratory measures
- vital signs
- ECG
- CTCAE Version 4.0 grades for laboratory and non-laboratory parameters.

10.6. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least one dose of the study drug and have had samples collected to allow the estimation of abemaciclib PK parameters.

Pharmacokinetic parameter estimates for abemaciclib will be calculated by standard noncompartmental methods of analysis using Phoenix WinNonlin on a computer that meets or exceeds the minimum system requirements for this program. The primary parameters for analysis will be C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$ of abemaciclib. Other noncompartmental parameters, such as $t_{1/2}$, CL/F, and V/F may be reported. The PK profiles will be graphically presented and summary statistics of PK parameters will be obtained.

Additional exploratory analyses will be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global Pharmacokinetic management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

10.7. Efficacy

Tumor response and progression will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Progression-free survival (PFS) time will be measured from the date of the first dose to the date of investigator-determined objective progression as defined by RECIST v1.1, or death from any cause. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment (if available) or date of the first dose if no post baseline radiographic assessment is available.

Overall survival (OS) duration will be measured from the date of the first dose to the date of death from any cause. For each patient who is not known to have died, OS will be censored at the date of last contact.

10.8. Planned Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least one dose of the study drug and have had samples collected to allow the estimation of abemaciclib PK parameters.

PK and safety analyses will be conducted after study completion.

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 and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

In this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

11.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites. 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 sites. The ERBs will review the protocol as required.

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

- the current IB or Patient Information Leaflet, Package Insert, Protocol, 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 International Conference on Harmonisation (ICH) Good Clinical Practices (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 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 investigator with the most enrolled patients will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

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.

12. References

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Attachment 1. Protocol JPBR Study Schedule

Study Schedule: Protocol I3Y-CR-JPBR

Cycle/Visit	Screening/ Baseline/0			Cycle 1									Cycle 2 and Beyond/2-X	Short-term Follow-up/801[l]	Long-term Follow-up /802-8XX[m]
Day relative to Day 1 in Each Cycle	**-25 to -1**	**-11 to -1**	**-7 to -1**	**1**	**2**	**3**	**4**	**11 ±2**	**18 ±2**	**25 ±2**	**31 -1**	**32 -1**	**28±2**		
Day after Last Dose														**30±7**	
Informed Consent[a]	X														
Medical History (including initial history/preexisting conditions/previous treatment)		X													
Pregnancy Test (if applicable)[b]			X												
Physical Exam		X							X			X	X	X	
Vital Signs[c] and Weight		X						X	X	X		X	X	X	
Height		X													
ECOG Performance Status		X										X	X	X	
ECG[d]			X	X							X		X		
Hematology/Serum chemistry[e]		X		X				X	X	X		X	X	X	
Blood PK Sampling[f]				X	X	X	X		X	X	X	X			
Tumor Measurement (Palpable and Visible)		X										X	X		X
Tumor Marker (if applicable) [g]		X											X		
Radiological Tumor Assessment[h]	X												X		X
Adverse Event Collection/CTCAE Grading[i]	X			X									X	X	X
Concomitant Medications	X			X									X	X	
Abemaciclib Therapy[j]				X			X[n]						X		
Patient Diary Dispense				X								X	X		
Patient Diary Collection												X	X		
Survival information[k]															X

Study Schedule: Protocol I3Y-CR-JPBR (concluded)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = Formalin-fixed paraffin-embedded; PD = progressive disease; PK = pharmacokinetic; Q12H = every 12 hours; SAE = serious adverse event.

[a] Informed consent form must be signed before performing any protocol procedure. Data obtained before patient's consent can be used as screening data if the relevant tests are conducted within the allowed time window.

[b] Females with child-bearing potential must have a negative serum pregnancy test within 7 days of the first dose of study drug (i.e., Day -7 to Day -1).

[c] Vital signs: Temperature, Pulse, Blood Pressure, Respiratory Rate

[d] ECGs of specified time point will be performed, collected, read/evaluated locally. ECGs should be performed at baseline (-7 days to -1 day before Cycle 1 Day 1), and the planned timing of predose, 4 hours, and 6 hours after study drug administration: Cycle 1, Day 1 and Day 31. See Attachment 5 for detailed time points.

[e] For baseline data, tests can be conducted within 3 days before the first dose of abemaciclib on Cycle 1, Day 1. The screening test results may be used as baseline data if the screening tests have been conducted within the allowed time window. During cycle2, in addition to Day 28, the tests will also be conducted on Day 15 (±2 days).

[f] PK sampling should be performed during Cycle 1 (Attachment 5).

[g] The frequency of tumor marker measurement is left to investigator.

[h] Radiological assessment is performed at baseline (Day -25 to Day -1), then in the last 7 days of every other cycle beginning with Cycle 2. For screening, scans performed prior to the date of consent may be used provided they are within 25 days of Cycle 1 Day 1. For patients who discontinue study treatment without objectively measured PD, continue to evaluate tumor response every 56 days (±7 days) by the same method used at baseline and throughout the study until the patient has objective disease progression, or until the study's final analysis. After the patient has objective disease progression, radiologic assessments are no longer required and the patient will be followed up approximately every 56 days (±14 days) until the patient's death or overall study completion.

[i] For details, see Section 8.1.2. Following the safety assessments in Visit 801, for patient with an AE 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.

[j] For details, see Section 7.2.1.

[k] Collection of survival data and subsequent antitumor therapies. Every 56 days (±14 days). Whenever possible, survival follow-up is conducted in person. If an in-person visit is not possible, the site may confirm survival by contacting the patient directly via phone.

[l] Short-term follow-up starts just after the last dose of study drug and ends when final safety assessments are completed (30 ±7 days after last dose of study drug).

[m] For patients who discontinue study treatment without objectively measured PD, continue to evaluate tumor response every 56 days (±14 days) by the same method used at baseline and throughout the study until the patient has objective disease progression, or until study completion. After the patient has objective disease progression, radiologic tests are no longer required and the patient will be followed up approximately every 56 days (±14 days) until the patient's death or overall study completion.

[n] For Cycle 1, single-dose abemaciclib will be given on Day 1 and Day 31, Q12H abemaciclib on Day 4, and then continuously until Day 30.

Attachment 2. Protocol JPBR Study Schedule – Continued Access Period

Procedure[a]	Treatment during Continued Access Period (every cycle)	30-Day Follow-Up[b] (+ 0-7d)
Visit	**501-5XX**	**901**
Toxicity Assessment/AEs	X	X
Abemaciclib Therapy	X	

Abbreviations: AE = adverse event; d = days.

a During continued access period, routine safety and efficacy monitoring, including radiographic evaluation of disease and laboratory testing, such as pregnancy testing, should be continued as necessary, and documentation retained within the source files, to confirm patient eligibility to continue on treatment or the 30-day short-term follow-up visit. The Sponsor will collect only data shown in this table for the continued access period.

b The short-term follow-up begins the day after the decision is made to discontinue study treatment and lasts approximately 30 days (no more than 37 days).

Attachment 3. Protocol JPBR Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology	**Clinical Chemistry**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Chloride
Mean cell hemoglobin concentration (MCHC)	Calcium
Leukocytes (WBC)	Albumin
Neutrophils	Total Protein
Lymphocytes	Blood Urea Nitrogen (BUN)
Monocytes	Creatinine
Eosinophils	Alkaline Phosphatase
Basophils	Alanine Aminotransferase (ALT)
Platelets	Aspartate Aminotransferase (AST)
	Total Bilirubin
Renal panel	**Serum Pregnancy Test (females with child-bearing potential only)**
Cystatin-C	

All tests will be assayed by local laboratory.

Attachment 4. Protocol JPBR
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 clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils	
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 Normalised Ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by local laboratory.

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

Attachment 5. Protocol JPBR Pharmacokinetic Sampling and ECG Schedule in Cycle 1

Pharmacokinetic Sampling and ECG Schedule in Cycle 1

PK Sample Number	Day in Cycle 1	Abemaciclib Dosing	Sampling Time for PK[a]	ECG[b]
1	1	X	Pre-dose (0 h)	X
2			1 h ± 10 min post-dose	
3			2 h ± 10 min post-dose	
4			4 h ± 20 min post-dose	X
5			6 h ± 20 min post-dose	X
6			8 h ± 30 min post-dose	
7			10 h ± 60 min post-dose[c]	
8	2	No dose	24 h ± 2 h post-dose	
9	3	No dose	48 h ± 2 h post-dose	
10	4	X	Pre-dose	
11	18 (±2)	X	Pre-dose (0 h)	
12	25 (±2)	X	Pre-dose (0 h)	
13	31 (-1)[d]	X	Pre-dose (0 h)	X
14			1 h ± 10 min post-dose	
15			2 h ± 10 min post-dose	
16			4 h ± 20 min post-dose	X
17			6 h ± 20 min post-dose	X
18			8 h ± 30 min post-dose	
19			10 h ± 60 min post-dose[c]	
20	32 (-1)[d]	No dose	24 h ± 2 h post-dose	

Abbreviations: CRFs = case report forms; ECG = electrocardiogram; PK = pharmacokinetic.

a The dose and dosing date for 3 days prior to PK sampling will be recorded in the CRFs.

b Perform prior to blood sampling for PK if the ECG is matched with PK sampling point. When ECGs and blood draws are obtained at the same time point, ECGs are completed first (within approximately 20 minutes prior to the PK sample).

c If patient constraints preclude collection of this 10-hour PK sample, omission of this sample will not constitute a protocol deviation.

d If the PK sampling of Day 31 is preceded with -1 day allowance (Day 30), the evening dose on Day 30 and the morning dose on Day 31 should be omitted and 24-hour PK sample will be collected on Day 31.

Attachment 6. Protocol JPBR
Example Inducers and Strong Inhibitors of CYP3A4

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

Inducers of CYP3A4

Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St. John's wort

Strong inhibitors of CYP3A4

Aprepitant
Ciprofloxacin
Clarithromycin
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Verapamil

Abbreviations: CYP = cytochrome P450; HIV = human immunodeficiency virus.

a All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated.

Attachment 7. Protocol JPBR Cytochrome P450 Substrates with Narrow Therapeutic Range

Cytochrome	Substrate
CYP1A2	Theophylline
	Tizanidine
CYP2C9	Warfarin
	Phenytoin
CYP2D6	Thioridazine
	Pimozide
CYP3A	Alfentanil
	Astemizole
	Cisapride
	Cyclosporine
	Dihydroergotamine
	Ergotamine
	Fentanyl
	Pimozide
	Quinidine
	Sirolimus
	Tacrolimus
	Terfenidine

Abbreviation: CYP = cytochrome P450.

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

Attachment 8. Protocol JPBR Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

When contacting Lilly to report an 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 9. Protocol JPBR ECOG Performance Status

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken et al. 1982.

Attachment 10. Protocol JPBR RECIST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable
Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable
All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements.. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the case record form (CRF) in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as one liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is should always be done rather than clinical examination unless the lesion(s) being followed

cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual

lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

Pet Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

Partial Response (PR): At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10mm short axis).

Non-CR/non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The Best Overall Response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 1. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 is to be used when patients have *nonmeasurable* disease only.

Table 2. Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease.
a non-CR/non-PD is preferred over SD for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6-8 weeks is reasonable. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from first dose.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Independent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Attachment 11. Protocol Amendment I3Y-CR-JPBR (e) Summary
A Phase 1 Study of Abemaciclib in Native Chinese Patients with Advanced and/or Metastatic Cancers

Overview

Protocol I3Y-CR-JPBR, a Phase 1 Study of Abemaciclib in Native Chinese Patients with Advanced and/or Metastatic Cancers, has been amended. The new protocol is indicated by Amendment (e) and will be used to conduct the study in place of any preceding version of the protocol.

Study JPBR protocol was amended to update the safety language regarding hepatic monitoring, assessment of renal function, and venous thromboembolic events (VTEs) for ongoing patients.

The amendment (d) revised the wording of enrollment and randomization. When the amendment was approved, the enrollment has already completed. The amended sections was not effective thus removed in this amendment (e).

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

The overall changes made to this protocol are as follows:.

- Section 2 remove the enrollment and randomization restriction
- Section 4 included VTE in abbreviations
- Section 7.2.3.1, Table JPBR.7.1 modified along with Sections 7.2.3.1.1, 7.2.3.1.2 and 7.2.3.1.2.1, and incorporated Section 7.2.3.1.2.2 for alignment with safety updates.
- Sections 8.1.4, 8.1.4.1, 8.1.4.2 and 8.1.4.3 incorporated safety monitoring language for hepatic conditions, renal function and VTEs.
- Attachment 6 and 7 CYPs text updated to align with abemaciclib program information

Revised Protocol Sections

Note: All deletions have been identified by ~~strikethroughs~~.

All additions have been identified by the use of underscore.

Synopsis

Study Design:

~~Based on the enrollment status, the study team decided that from 17-May-2018 onwards, all patients who meet the enrollment criteria will be assigned to receive 150 mg abemaciclib and thus randomization will no longer be applied.~~ Analysis on available PK and safety data will be conducted after study completion.

Section 4. Abbreviations…

VTE	venous thromboembolic event

6.2. Summary of Study Design

~~Based on the enrollment status, the study team decided that from 17-May-2018 onwards, all patients who meet the enrollment criteria will be assigned to receive 150 mg abemaciclib and thus randomization will no longer be applied.~~ Analysis on available PK and safety data will be conducted after study completion.

7.2.3 Does Ajustments and Delays

Table JPBR.7.1. Toxicity Dose Adjustments and Delays of Study Drug for Study JPBR

Cause	Profile and Severity	Dose Suspension	Dose Reduction
…			
Hematologic Toxicity:If p~~P~~**atient requires administration of blood cell growth factors** Section 7.2.3.1.1	Regardless of severity (~~Growth factors~~ U~~u~~se of growth factors according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by one dose level unless already performed for incidence of toxicity that led to the use of growth factor
Nonhematological Toxicity[b] (except diarrhea and ALT increased) Section 7.2.3.1.2	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose ~~**MAY**~~**MUST** be suspended~~.~~ until toxicity resolves to either baseline or Grade 1.	Dose ~~**MAY**~~ **MUST** be reduced by one dose level.

Nonhematological Toxicity Section 7.2.3.1.2	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by one dose level.
~~Diarrhea~~ ~~Section 7.2.3.1.2.1~~	~~Requiring hospitalization or Grade 3 or 4~~	~~Dose **MUST** be suspended until toxicity resolves to at least Grade 1.~~	~~Dose **MUST** be reduced by one dose level.~~
Diarrhea Section 7.2.3.1.2.1 and 7.5.1	Grade 2 that does not resolve ~~with maximal supportive measures~~ within 24 hours to at least Grade 1	Dose ~~**SHOULD**~~**MUST** be suspended until toxicity resolves to at least Grade 1.	Dose ~~**MAY** be reduced by one dose level.~~ reduction is NOT required.
Diarrhea Section 7.2.3.1.2.1 and 7.5.1	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures ,or any Grade of diarrhea that requires hospitalization ~~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 one dose level.
Diarrhea Section 7.2.3.1.2.1 and 7.5.1	Grade 3 or 4	Dose MUST be suspended until toxicity resolves to at least Grade 1.	Dose MUST be reduced by one dose level.
ALT Increased (Sections 7.2.3.1.1.2. and 8.1.2.1)	Persistent or recurrent[a] Grade2 (>3.0-5.0×ULN), or Grade 3 (>5,0-20.0×ULN)[c]	Dose MUST be suspended until toxicity resolves to baseline or Grade 1.	Dose MUST be reduced by 1 dose level.
ALT Increased (Sections 7.2.3.1.1.2. and 8.1.2.1)	Grade 4 (>20.0×ULN)	Study drug MUST be discontinued.	Study drug MUST be discontinued.
ALT Increased with increased total bilirubin, in the absence of cholestasis (Sections 7.2.3.1.2.2.)	Grade 3 increased ALT (>5.0 x ULN) with total bilirubin >2 x ULN	Study drug MUST be discontinued	Study drug MUST be discontinued

Abbreviation: ALT = alanine transaminase; ASCO = American Society of Clinical Oncology.
Note: MUST = mandatory.

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

- shows stable hematological counts (Grade ≤2) during that timeframe
- has absence of any signs or risk of infection
- is benefiting from study treatment

b Additional guidance for renal and hepatic monitoring is in Sections 8.1.4.1 and 8.1.4.2.

c Grade 3 ALT increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 8.1.4.1 for additional guidance for hepatic monitoring

7.2.3.1.1 Hematologic Toxicity

If the patient experiences a recurrent episode of Grade 3 hematologic toxicity, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of the study must be reduced by one dose level as outlined in Table JPBR.7.2.

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

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

7.2.3.1.2. Nonhematological Toxicity

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea; refer to Section 7.2.3.1.2.1 or ALT increased, refer to Section 7.2.3.1.2.2) possibly related to abemaciclib that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, then dosing ~~may~~must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib ~~may~~must be reduced as outlined in Table JPBR.7.2.

7.2.3.1.2.1. Diarrhea

If a patient experiences persistent or recurrent diarrhea (Grade 2) that does not resolve with maximal supportive measures (refer to Section 7.5.1) within 24 hours to either baseline or at

least Grade 1, then study treatment ~~should~~must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib ~~may~~must be reduced by one dose level as outlined in Table JPBR.7.2 ~~at the discretion of the investigator. If the same dose level was resumed and diarrhea recurs despite maximal supportive measures, the dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib must be reduced again as outlined in Table JPBR.7.2~~.

7.2.3.1.2.2. Hepatic Toxicity

Dose modifications and management for increased ALT are provided in Table JPBR.7.1. For persistent or recurrent Grade 2 ALT increased that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1, or Grade 3 ALT increased, blinded study drug must be suspended until the toxicity has resolved to at least Grade 1 and the dose must be reduced by 1 dose level. Discontinue blinded study drug for Grade 3 increased ALT (>5.0 x ULN) with total bilirubin >2 x ULN, in the absence of cholestasis. For Grade 4 ALT increased, the patient must be discontinued from blinded study drug. Refer to Section 8.1.4.1 for additional hepatic monitoring guidance.

7.3. Method of Assignment to Treatment

~~Based on the enrollment status, the study team decided that from 17-May-2018 onwards, all patients who meet the enrollment criteria will be assigned to receive 150 mg abemaciclib and thus randomization will no longer be applied.~~

8.1.2. Adverse Events

The investigator will record all relevant AE/SAE information in the CRF. Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, study drug via CRF.

8.1.2.1 Serious adverse Events

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. An SAE is any adverse event during this study that results in one of the following outcomes:

8.1.4. Safty Monitoring

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,
- adverse events,
- ~~If a study patient experiences elevated ALT ≥5X upper limit of normal (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/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 4).~~

8.1.4.1 Special Hepatic Safety Data Collection

If a study patient experiences elevated ALT ≥5×ULN and elevated total bilirubin (TBL)≥2×ULN, or ALT >8x ULN for patients with underlying baseline hepatic metastases, liver tests (Attachment 4), including ALT, AST, TBL, direct bilirubin, gamma glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests (Attachment 4) and in consultation with the Lilly CRP. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels. Additional diagnostic testing should be considered to rule out cause of increased liver enzymes per the investigator's discretion.

Hepatic monitoring tests (Attachment 4) should be collected in the event that 1 or more of the following conditions is met for the patient during the course of the study:

- ALT ≥5×ULN and TBL ≥2×ULN
- ALT>8x ULN for patients with underlying hepatic metastasis
- discontinuation from study treatment due to a hepatic event or an abnormality of liver tests

8.1.4.2 Renal Function

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

Dose adjustment (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for non-hematological toxicities (Table JPBR.7.1).

8.1.4.3 Venous Thromboembolic Events

In the randomized Phase 3 studies in breast cancer patients who received abemaciclib in

combination with endocrine therapy, there was a greater number of patients who experienced VTEs in the abemaciclib plus endocrine therapy arm than in the placebo plus endocrine therapy arm. The majority of the events were non-serious and were treated with low-molecular-weight heparin. Generally, these events did not result in discontinuation of the study treatment. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. For suspected or confirmed VTE (eg. deep vein thrombosis or pulmonary embolism), treatment should occur according to usual clinical practice.

Attachment 6 Protocol JPBR Example Inducers and Strong Inhibitors of CYP3A4

Strong inhibitors of CYP3A4
~~All HIV protease inhibitors~~
Aprepitant
Ciprofloxacin
Clarithromycin
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Verapamil

Attachment 7 Protocol JPBR Cytochrome P450 Substrates with Narrow Therapeutic Range

Cytochrome	Substrate
CYP1A2	Theophylline
	Tizanidine
~~CYP2C8~~	~~Paclitaxel~~