STUDY OF PALBOCICLIB IN COMBINATION WITH LETROZOLE AS TREATMENT OF POSTMENOPAUSAL WOMEN WITH HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE ADVANCED BREAST CANCER FOR WHOM LETROZOLE THERAPY IS DEEMED APPROPRIATE

Compound:	PD-0332991
Compound Name:	Palbociclib
United States (US) Investigational New Drug (IND) Number:	[redacted]
European Clinical Trials Database (EudraCT) Number:	Not Applicable
Protocol Number:	A5481053
Phase:	Phase 3

[redacted]

Document History

Document	Version Date	Summary of Changes
Original protocol	23 July 2015	Not applicable (N/A)

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APPENDICES

SCHEDULE OF ACTIVITIES

The schedule of activities table (Table 1) provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES (Section 6) and ASSESSMENTS (Section 7) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

Table 1. Schedule of Activities

Visit Identifier	Screening[a]	Treatment: One cycle = 28 days[b]			End of Treatment[d]	End of Study[d]
		Cycles 1 and 2		Cycles ≥3		
Study day	**Within 28-30 days prior to randomization unless specified otherwise**	**Day 1[c]**	**Day 14**	**Day 1**		
Time window		**±2 days**	**±2 days**	**±2 days**		
Procedures at Screening						
Informed consent[e]	X					
Eligibility criteria evaluation[f]	X					
Registration[g]	X					
Medical/Oncological history[h]	X					
Procedures at Screening and on study						
Physical examination[i]	X	Per routine clinical practice				
ECOG performance status[j]	X	Per routine clinical practice			X	
12-Lead ECG[k]	X	As clinically indicated				
Treatments						
Palbociclib (PD-0332991[l])		Orally once daily from Day 1 to Day 21 of each cycle (Schedule 3/1)				
Letrozole[m]		Orally once daily (Schedule: continuous dosing)				
Clinical Assessments						
Tumor assessment (CT or MRI scans) [n]	X	Per routine clinical practice				
Adverse events[o]	X	X				X
Hematology (platelet count, ANC, WBC count, hemoglobin) [p]	X	X	X	X	X	
HbA1c[q]	X	Every 3 months			X	
Blood chemistry[r]	X	Per routine clinical practice				

Abbreviations: ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; CT=CAT scan; MRI=magnetic resonance imaging; ANC=absolute neutrophil count; WBC=white blood cell; HbA1c=Glycated hemoglobin.

a. **Screening:** All assessments should be performed within 28-30 days prior to study randomization.

b. **Active Treatment Phase:** All assessments should be performed prior to dosing with study medications on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. Clinical visits will be conducted as per local practice and as clinically indicated. Each subsequent cycle will begin 7 days after the last dose of study drug in the prior cycle to allow patients a 7-day washout period for each cycle.

c. **Cycle 1/Day 1:** Blood chemistry and hematology not required if acceptable screening assessment is performed within 7 days prior to randomization.

d. **End of Treatment/End of Study:** The End of Treatment (EOT) visit will be conducted when palbociclib is permanently discontinued for any reason. The indicated assessments are to be obtained if not completed in the last week of therapy. Patients who permanently discontinue palbociclib for any reason will also complete an End of Study (EOS) visit that will occur 28 days after last dose of palbociclib. An EOS visit will be completed if a patient will continue on commercial palbociclib. Adverse events should be followed up until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable".

e. **Informed Consent**: Must be obtained prior to undergoing any study specific procedures.

Table 1. Schedule of Activities

Visit Identifier	Screening[a]	Treatment: One cycle = 28 days[b]			End of Treatment[d]	End of Study[d]
		Cycles 1 and 2		Cycles ≥3		
Study day	Within 28-30 days prior to randomization unless specified otherwise	Day 1[c]	Day 14	Day 1		
Time window		±2 days	±2 days	±2 days		

f. **Eligibility Criteria Evaluation:** Patients must meet all of the eligibility criteria in the protocol.

g. **Registration:** Patient identification number will be attributed to each patient. Patients will be assigned a single subject identification number (SSID) which will be obtained at the time of screening using the automated registration system and retained throughout the study. A separate randomization number will be assigned by the automated registration system at Cycle 1 Day 1 and will be recorded on the CRF.

h. **Medical/Oncologic History:** Medical history includes history of disease process other than oncology (active or resolved). Oncological history includes date of primary diagnosis, information on prior antitumor treatments and radiotherapy, and oncologic surgeries.

i. **Physical Examination:** General clinical examination of major body systems. To be performed at Screening, and as per routine clinical practice during the treatment.

j. **ECOG Performance Status**: To be performed at Screening, as per routine clinical practice during the treatment, and at EOT. ECOG performance status scale is available in Appendix 1.

k. **12-Lead ECG**: Three consecutive 12-lead ECGs will be performed approximately 2 minutes apart at Screening to verify eligibility. ECG to be repeated during the treatment, as clinically indicated. If the mean QTc is prolonged (value of >500 msec), then the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Only ECG at Screening will be recorded on the CRF (Case Report Form).

l. **Palbociclib Administration:** PD-0332991 will be administered orally once daily at the starting dose of 125 mg on Day 1 to Day 21, followed by 7 days off treatment (Schedule 3/1). The patient will receive drug supply at the clinical site that will be sufficient to last until their next cycle visit.

m. **Letrozole Administration:** Letrozole will be administered orally once daily at the dose of 2.5 mg (continuous daily dosing schedule). Locally obtained commercial supplies of letrozole will be used

n. **Tumor Assessments:** Tumor assessments are to be performed at Screening as per local practice and according to the patient's clinical status thereafter. Tumor assessment evaluation will be conducted as per local guidelines. Only investigator's assessments will be recorded on the CRF.

o. **Adverse Events**: Patients must be followed for adverse events (AEs) from the time they signed the informed consent until 28 days after the last treatment administration or until all palbociclib-related toxicities have resolved, whichever is later. AEs (serious and nonserious) should be recorded on the CRF from the time the patient has taken at least 1 dose of investigational product through the patient's last visit. AEs should be documented and recorded at each clinical visit using NCI CTC-AE version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent through and including 28 calendar days after the last administration of the investigational product. SAEs experienced by a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

p. **Hematology:** To include platelet count, absolute neutrophil count (ANC), white blood cell (WBC) count, and hemoglobin. To be performed to check patient's eligibility at Screening, every 2 weeks (Days 1 and 14) of the first 2 cycles, then monthly on Day 1 of each subsequent cycle of treatment with palbociclib and at EOT. In the case of Grade ≥3 neutropenia consider repeating complete blood count monitoring 1 week later in accordance with best local practice and report on the CRF in order to document the ANC value at the time of severe neutropenia as well as the time to recovery of neutrophils to ≥1000 cells/mm3. Re-treatment criteria are based on time to recovery of neutrophil count. For patients who develop Grade 3 or 4 neutropenia, refer to the dose modifications described in Table 6. If granulocyte-colony stimulating factors (G-CSF) and/or antibiotics are administered, their use will be documented on the CRF.

q. **Glycated Hemoglobin (HbA1c):** To be assessed at Screening, every 3 months, and EOT, and will be documented on the CRF.

r. **Blood Chemistry:** To be performed to check patient's eligibility at Screening and as per routine clinical practice thereafter. Only laboratory data at Screening will be recorded on the CRF.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Palbociclib is being developed for the treatment of hormone receptor-positive (HR-positive), HER2-negative (human epidermal growth factor receptor 2 negative) breast cancer (BC).

1.2. Background and Rationale

HR-positive/HER2-negative BC is the most common subset of breast cancer.[1] Most patients are diagnosed at an early stage and remain relapse-free if treated with a prolonged course of endocrine therapy. However, about one third of patients with HR-positive/HER2-negative tumors, diagnosed initially with early stage disease, experience disease recurrence.[2] The fundamental problem is that endocrine agents are only partially effective, typically causing cell cycle arrest and tumor dormancy rather than true cure.

The role of estrogens in BC etiology and progression is well established. Modification of estrogen activity or synthesis represents the treatment of choice for postmenopausal women with HR-positive advanced breast cancer (ABC), particularly for those with slowly progressive disease and limited tumor-related symptoms.[3] Studies of estrogen receptor (ER)-positive BC cell lines indicate that estrogens[4] and antiestrogens[5] act on sensitive populations of cells in early to mid-G1 phase. G1/S transition is under the control of cyclin-dependent kinases (CDKs) activated by specific complex formation with regulatory cyclins.

Conversion of androgens to estrogens via aromatase enzyme action represents the main source of estrogens in postmenopausal women. Letrozole is an oral nonsteroidal aromatase inhibitor that is approved worldwide for the first line treatment of postmenopausal women with HR-positive ABC. Letrozole is administered orally in a continuous regimen at a 2.5-mg daily dose. In a multicenter Phase 3 study in patients with HR-positive or HR-unknown ABC, letrozole was superior to tamoxifen for time to progression, time to treatment failure, overall objective response rate, and overall clinical benefit response.[6] Multiple clinical studies have shown that letrozole is well tolerated.

Palbociclib is an oral, selective, CDK 4/6 inhibitor that has been under investigation in clinical trials in multiple indications. Palbociclib inhibits cell proliferation by preventing cell cycle progression from G1 to S phase and has demonstrated antitumor activity in multiple preclinical models, including ER-positive luminal breast cancer cell lines.

Furthermore, preclinical exploration using a BC cell line panel demonstrated the presence of retinoblastoma (Rb) protein and upregulation of cyclin D1 as well as decreased CDKN2A (p16) being associated with sensitivity to palbociclib as well as with its effects upon cell cycle and growth inhibition. These gene expression findings were also associated with the luminal subtype versus basal-like subtype of BC.

These results, together with published data on the known interaction of estrogens and CDKs and the important role of cell cycle-related proteins in the genesis and maintenance of BC, led to the initiation of a randomized Phase 2 clinical trial (A5481003 study; PALOMA-1) investigating the antitumor activity of palbociclib in combination with letrozole and single-agent letrozole in the first-line treatment of ER-positive/HER2-negative ABC patients. The final analysis of this study demonstrated a consistent trend of clinically meaningful improvements in progression-free survival (PFS, the primary endpoint) and response based secondary endpoints,[7] and the study results led to the approval of palbociclib for advanced BC by the US Food and Drug Administration (FDA) on 03 February 2015.

1.3. Palbociclib

Oral palbociclib is a novel, first-in-class highly selective reversible inhibitor of cyclin-dependent kinases (CDK) 4 and 6 that is being studied for use in the treatment of cancer. The compound inhibits cell proliferation by preventing progression of the cell cycle from G1 into the S phase.

1.3.1. Preclinical Data

Palbociclib inhibits purified CDK4-catalyzed phosphorylation of retinoblastoma protein with an IC_{50} of less than 20 nm, and also tumor growth of several types of human xenograft tumors (SF-295, MDA-MB-435, Colo-205, and others) grown in mice.

Treatment of cultured tumor cells with palbociclib causes growth arrest that is accompanied by the inhibition of specific retinoblastoma (Rb) phosphorylation by CDK4 or CDK6 on residues serine -780 and -795 of Rb. Consequently, the phosphorylation status of these sites serves as specific biomarkers of CDK4/6 inhibition by palbociclib. Estimated steady-state plasma concentrations of 1000 ng/mL resulted in 80% to 90% inhibition of phospho-Rb formation and 50% reduction of tumor growth. Reduction in phospho-Rb was rapidly reversible as plasma palbociclib concentrations declined.

Palbociclib was tested in vitro on molecularly characterized human BC cell lines. Results from these experiments indicate that those cell lines that are more sensitive to palbociclib (IC_{50} <150 nm) have low levels of CDKN2A (p16) and high levels of Rb1, while resistant cell lines show the opposite characteristics. Sensitive cell lines in this panel represent mostly the luminal ER-positive subtype.[8] The combination of palbociclib and aromatase inhibitors has not been tested in preclinical models. However, the combination of palbociclib with tamoxifen has recently been tested in vitro in ER-positive human BC cell lines indicating a synergistic interaction[7] and provides a biologic rationale for evaluating the combination of palbociclib with antihormonal therapy in the clinic.

Palbociclib preclinical data indicate that it may be expected to have a direct effect on growth arrest as well as potential secondary cytotoxic activity.

1.3.1.1. Ocular Preclinical Data

Preliminary results from an ongoing 27-week repeat-dose oral toxicity study with palbociclib in rats identified a potential nonclinical safety finding related to the eye. Animals were evaluated by indirect ophthalmoscopy and by slit lamp biomicroscopy predose and prior to

termination. The available data suggests that the cataracts observed in both male and female rats are palbociclib-related. Exposures in this nonclinical study are comparable to clinical exposures at the recommended human dose of 125 mg once daily (QD).

The mechanism for cataract formation in palbociclib-treated rats is unknown; however, its pathogenesis may be related to primary pharmacology. CDK4 expression (mRNA and protein) has been identified in the lens epithelial layer and in lens fibers of rats, suggesting its importance to lens fiber differentiation.[9] Altered cell growth of the lens epithelium is also recognized as a potential mechanism for cataract formation.[10] As CDK 4 and 6 expressions have also been identified in the human lens epithelial cell,[11] a potential risk for cataract formation in patients who received palbociclib cannot be completely excluded.

A review of the Pfizer safety database for cases received through 14 January 2014 identified no serious cases from clinical studies or other solicited sources. The adverse event (AE) cataract has been reported in 2 patients (1 Grade 2 and 1 Grade 3) out of approximately 400 patients who received palbociclib in Pfizer-sponsored studies. Neither event was considered serious, nor related to palbociclib; both patients had other identifiable risk factors for cataracts, such as age and long-term corticosteroid use. Both patients continued on treatment for 16-18 months beyond the diagnosis of cataract.

Based on the limited preclinical and clinical data currently available, it is not known whether true clinical risk exists for palbociclib-associated cataracts. In order to assess this potential risk in detail, the Phase 3 Studies A5481008 and A5481023 were amended to implement prospective ophthalmic assessments in all newly enrolled patients. In addition, ophthalmic assessments will be collected in all patients who will be enrolled in the Phase 3 Study A5481027. The results of the ophthalmic assessments will provide a better understanding of the risk of ocular adverse events and will provide information to determine whether further actions are warranted.

1.3.1.2. Cataracts and Other Eye Disorders; Relationship of Cataracts to Hyperglycemia-Related Events

Cataracts/lens degeneration was identified in nonclinical studies in rats in association with altered glucose metabolism (glycosuria and/or hyperglycemia) following 27 weeks of intermittent dosing (a scheduled dosing regimen of 3 weeks of consecutive daily dosing followed by a 1-week nondosing period). A further association was found between glucose metabolism and pancreatic islet vacuolation. Investigatory analysis of the data from the 27-week rat study indicated that the islet cell vacuolation involved beta cells including beta cell depletion, with corresponding decreases in serum insulin and C-peptide. Reversibility was not established for the changes in glucose homeostasis or the effects on the pancreas and eye following a 3-month recovery period. Alterations of glucose metabolism, pancreatic histopathology, or cataracts/lens degeneration were not identified in dogs in studies up to 39 weeks in duration.

Review of all available laboratory data from the first-in-patient Study A5481001 has not suggested any apparent effect of duration of palbociclib exposure or palbociclib dose on glucose levels and consequently development of cataracts.

Cataract was experienced by 2 patients with advanced breast cancer receiving palbociclib plus letrozole in Study A5481003 as of 02 January 2015. These events were considered to be unrelated to study treatment. In addition, these events were experienced by patients who had not experienced hyperglycemia-related events.

In summary, based on a careful review of the available clinical data, there is currently insufficient evidence that palbociclib is causally related to the development of hyperglycemia and cataracts in humans.

1.3.2. Palbociclib Clinical Activity

Palbociclib has been tested in a Phase 1 dose-escalation Study A5481001 in 74 patients with advanced cancer. Two dosing schedules were evaluated: Schedule 3/1 (3 weeks on treatment/1 week off treatment) and Schedule 2/1 (2 weeks on treatment/1 week off treatment). All dose-limiting toxicities (DLTs) observed in this study were related to myelosuppression and mainly consisted of Grade 3 neutropenia lasting more than 7 days after the end of the treatment cycle. However, neutropenia was reversible and noncumulative. A greater proportion of patients on the 2/1 schedule had treatment-related adverse events during and after Cycle 1 than patients on the 3/1 schedule although the proportion of patients with treatment-related neutropenia was similar with respect to the 2 dosing schedules, both during and after Cycle 1. Based on the relatively improved safety profile of Schedule 3/1, and the efficacy results from this study, the Schedule 3/1 has been selected for further clinical development and the recommended dose for this schedule was determined to be 125 mg once daily. This schedule and associated dose was further explored in combination with letrozole in the Phase 1/2 study in patients with ABC described below.

1.4. Study Rationale

The purpose of this study is to provide access to palbociclib in Mexico and in selected Latin American countries before it becomes commercially available to patients with HR-positive/HER2-negative ABC who are appropriate candidates for letrozole therapy.

Complete information for palbociclib may be found in the Single Reference Safety Document (SRSD), which for this study is the palbociclib Investigator's Brochure (IB).

The FDA approved label for letrozole[12] is the SRSD for letrozole.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

- To provide access to palbociclib in Mexico and in selected Latin American countries to postmenopausal patients with hormone receptor-positive (HR-positive), HER2-negative ABC who are deemed appropriate for letrozole therapy.

Secondary Objectives

- To gain additional safety data of the combination of palbociclib with letrozole in the postmenopausal HR-positive/HER2-negative population.

- To gain additional antitumor activity data of the combination of palbociclib with letrozole in the postmenopausal HR-positive/HER2-negative population.

2.2. Endpoints

Adverse events as characterized by type, frequency, severity (as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.03), and seriousness.

Death from any cause while on treatment and within 28 days of palbociclib discontinuation.

Tumor response (based on investigator assessment reported on Case Report Form [CRF]).

3. STUDY DESIGN

A multicenter, single-arm, open-label clinical trial will be conducted in Mexico and in selected Latin American countries.

Eligible patients will be postmenopausal women with HR-positive and HER2-negative ABC. Patients will have a histologically or cytologically proven diagnosis of adenocarcinoma of the breast (locoregionally recurrent or metastatic disease) and will be candidates to receive letrozole for their advanced disease as first- or later lines of treatment.

Approximately 130 patients will be enrolled. This total number of patients will allow for enrollment of an adequate number of patients from each participating country. Patients will continue to receive treatment with palbociclib until disease progression, symptomatic deterioration, unacceptable toxicity, death, withdrawal of consent, or time of commercial availability of palbociclib, whichever occurs first.

Upon marketing approval of palbociclib by the local health authorities in the participating countries, patients enrolled in Study A5481053 will end participation in this study and be moved to commercially available palbociclib (if considered to be appropriate by the investigator), as soon as feasible.

Patients will undergo AE monitoring as per local practice and per protocol. All grade, all-causality AEs and all serious adverse events (SAEs) will be recorded on the CRF. All deaths occurring up to 28 days after palbociclib is discontinued will be recorded.

Hematology laboratory data will be recorded every 2 weeks for the first 2 cycles of therapy, then monthly at the start of each cycle thereafter. In the case of Grade ≥3 neutropenia, consider repeating complete blood count monitoring 1 week later in accordance with best local practice and report on the CRF in order to document the level of neutropenia and the time to recovery of neutrophils to ≥1000 cells/mm^3. Re-treatment criteria are based on time to recovery of neutrophil count. For patients who develop Grade 3 or 4 neutropenia, refer to the dose modifications described in Table 6. The clinical actions taken as a result of Grade ≥3 neutropenia, including the use of granulocyte colony stimulating factor (G-CSF), if any, should be recorded.

Tumor response will be assessed as per local practice and only investigator tumor assessments will be collected. The date of tumor progression will be recorded.

When patients are moved to commercial supply of palbociclib, their participation in the study and clinical study data collection will be discontinued.

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Women ≥18 years of age with proven diagnosis of advanced adenocarcinoma of the breast (locoregional recurrent or metastatic disease).
2. Women who are not of childbearing potential (ie, meet at least 1 of the following criteria):
    a. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    b. Have medically confirmed ovarian failure; or
    c. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathologic or physiologic cause; and have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state.

3. ER-positive and/or Progesterone receptor (PgR)-positive tumor based on local laboratory results (test as per local practice).

4. HER2-negative breast cancer based on local laboratory results (test as per local practice or local guidelines).

5. Patients must be appropriate candidates for letrozole therapy.

6. Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (see Appendix 1).

7. Adequate bone marrow function:

   a. Absolute Neutrophil Count (ANC) $\geq 1500/mm^3$ ($1.5 \times 10^9/L$);

   b. Platelets $\geq 100{,}000/mm^3$ ($100 \times 10^9/L$);

   c. Hemoglobin ≥9 g/dL (90 g/L).

8. Adequate liver function:

   a. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤3 x Upper Limit of Normal (ULN) (≤5.0 x ULN if liver metastases present);

   b. Alkaline phosphatase ≤2.5 x ULN (≤5.0 x ULN if bone or liver metastases present);

   c. Total serum bilirubin ≤1.5 x ULN (≤3.0 x ULN if Gilbert's disease).

9. Adequate renal function:

   a. Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≥60 mL/min.

10. Resolution of all acute toxic effects of prior therapy, including radiotherapy to Grade ≤1 (except toxicities not considered a safety risk for the patient) and recovery from surgical procedures.

11. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

12. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Known hypersensitivity to letrozole, or any of its excipients, or to any palbociclib excipients.

2. Current use of food or drugs known to be potent inhibitors or inducers of CYP3A4 isoenzymes within 7 days prior to study entry (see Prohibited Medications, Section 5.7.1).

3. Prior treatment with any CDK inhibitor.

4. Previous participation in a palbociclib clinical study.

5. Participation in other studies involving investigational drug(s) within 2 weeks prior to study entry and/or during study participation.

6. QTc >480 msec; history of QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes.

7. High cardiovascular risk, including, but not limited to recent myocardial infarction, severe/unstable angina and severe cardiac dysrhythmias in the past 6 months prior to enrollment.

8. Diagnosis of any second invasive malignancy within the last 3 years prior to enrollment. Note: patients with adequately treated basal cell or squamous cell skin cancer, a history of intraepithelial neoplasia or in situ disease (eg, carcinoma in situ of the cervix or melanoma in situ) may enter.

9. Active uncontrolled or symptomatic brain metastases. Previously treated and clinically stable, brain metastases are permitted.

10. Other severe acute or chronic medical or psychiatric conditions:

    a. Including recent (within the past year) or active suicidal ideation or behavior, or

    b. Laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

11. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

4.3. Sponsor's Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the study is documented in the study contact list .

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient (palbociclib) being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Allocation to Treatment

Patients will be assigned a single subject identification number (SSID) which will be obtained at the time of screening using the automated registration system and retained throughout the study. A separate randomization number will be assigned by the automated registration system at Cycle 1 Day 1 and will be recorded on the CRF.

5.2. Patient Compliance

Patients will be required to return all bottles of palbociclib at the beginning of each cycle for drug accountability.

Drug accountability will be performed at every clinical visit prior to dispensing drug supply for the next cycle. The number of remaining capsules will be collected, documented, and recorded to assess compliance.

5.3. Investigational Product Supplies

The investigational product used in the course of this trial is palbociclib (PD-0332991).

5.3.1. Dosage Form(s) and Packaging

5.3.1.1. Palbociclib

Palbociclib will be supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base. The oral drug formulation will be supplied in High Density Polyethylene (HDPE) bottles containing 75-mg, 100-mg, or 125-mg capsules. The capsules can be differentiated by their size and color (Table 2).

Table 2. Palbociclib Capsule Characteristics

Dosage	Capsule Color
75 mg	Sunset Yellow/Sunset Yellow
100 mg	Caramel/Sunset Yellow
125 mg	Caramel/Caramel

5.3.1.2. Letrozole

Commercially available letrozole will be provided. Locally obtained commercial supplies of letrozole will be used in accordance with local regulations.

5.3.2. Preparation and Dispensing - Palbociclib

The patient number should be recorded on the bottle label in the spaces provided by qualified site personnel at the time of assignment to the patient. Qualified site personnel must ensure that patients clearly understand the directions for self-medication.

Patients should be given a sufficient supply to last until their next cycle. Only a single capsule strength will be dispensed to the patient at each dispensing visit.

Please note that bottles contain 23 capsules, but only up to 21 will be taken in a given cycle. Patients should be advised of this to avoid confusion.

Unused drug and/or empty bottles should be returned to the site at the next cycle. Unused returned medication MUST NOT be re-dispensed to patients.

In the event of dose modification, a request should be made of the patient to return all previously dispensed medication to the clinic and new capsules will be dispensed.

Palbociclib is an agent that must be handled and administered with care. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

5.4. Administration

5.4.1. Palbociclib

Palbociclib will be administered orally once a day at 125 mg/day for 21 days followed by 7 days off treatment for each 28-day cycle (Schedule 3/1).

General rules for palbociclib administration:

- Palbociclib should be taken with food.
- Palbociclib capsules should be swallowed whole (do NOT manipulate or chew, crush, or open them prior to swallowing).
- No capsule should be ingested if it is broken, cracked, or otherwise not intact.
- Patients should be encouraged to take their dose at approximately the same time each day.
- Patients who miss a day's dose entirely must be instructed NOT to "make it up" the next day.
- Patients who vomit any time after taking a dose must be instructed NOT to "make it up" and to resume treatment the next day as prescribed.
- Patients who inadvertently take 1 extra dose during a day must be instructed to skip the next day's dose. Also refer to the Medication Errors, Section 8.4 for further details on medication errors and overdose.

5.4.2. Letrozole

Letrozole will be administered orally at 2.5 mg once daily as a continuous daily dosing schedule, according to product labeling and in compliance with its local prescribing information.

5.4.3. Recommended Dose Modification

In the event of significant treatment-related toxicity, administration of palbociclib may need to be adjusted as described in the following sections. As the letrozole dose cannot be reduced, letrozole treatment may be interrupted in the case of toxicity as described below.

Depending on the nature of the toxicity observed, treatment interruption may be required for 1 or both study drugs in the combination. In the event treatment interruption is deemed necessary for just 1 of the study drugs in the combination, treatment with the other drug may continue as planned if deemed clinically appropriate.

In case of palbociclib dose delays, administration of letrozole may continue according to the preplanned schedule.

In case of palbociclib permanent discontinuation, the patient will undergo end of treatment (EOT) and end of study (EOS) visits as described in Schedule of Activities (Table 1). Continuation of letrozole would be off study per treating physician discretion.

5.4.3.1. Dosing Interruptions/Delays - Recommendations for Palbociclib

Patients experiencing the following adverse events may have their treatment with palbociclib interrupted/delayed until criteria for re-treatment are met (Section 5.4.3.2).

Table 3. Adverse Events Leading to Dose Interruption/Delay

Hematologic toxicity of Grade ≥3
Non-hematologic toxicity of Grade ≥3 *(including nausea, vomiting, and diarrhea only if persisting despite optimal medical treatment)***.**

Patients should not hold or discontinue palbociclib for non-hematologic side effects potentially or likely related to concomitant letrozole therapy (eg, Grade 3 or long lasting Grade 2 joint pain) as per the investigator's judgment.

Depending on when the adverse event resolves, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay in the initiation of the subsequent cycle.

Doses omitted for toxicity are not replaced within the same cycle.

Doses should be held until toxicity resolution as per Re-treatment Criteria (Section 5.4.3.2).

The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Dose Reductions (Section 5.4.3.3).

In the case of Grade ≥3 neutropenia, consider repeating complete blood count monitoring 1 week later in accordance with best local practice and report on the CRF in order to document the level of neutropenia and the time to recovery of neutrophils to ≥1000 cells/mm^3. Re-treatment criteria are based on time to recovery of neutrophil count. For patients who develop Grade 3 or 4 neutropenia, refer to the dose modifications described in Table 6. The clinical actions taken as a result of Grade ≥3 neutropenia, including the use of G-CSF, if any, should be recorded.

If a dose reduction is applied in the same cycle, the patient will need to return to the clinic to receive new drug supply.

5.4.3.2. Re-Treatment Criteria - Palbociclib

Re-treatment with palbociclib, following treatment interruption for treatment-related toxicity, may not occur until all of the following parameters have been met:

Table 4. Palbociclib Re-Treatment Criteria

Platelet count ≥50,000/mm^3
ANC ≥1000/mm^3 and no fever
Grade ≥3 non-hematologic AEs (including nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment) have recovered to Grade ≤1 or baseline or, at the investigator's discretion, Grade ≤2 if not considered a safety risk for the patient.
QTc ≤500 msec and potential reversible causes (eg, electrolyte imbalance, concomitant medications known to prolong QTc) corrected.*   **If QTc remains >480 msec, treatment may re-start but the electrocardiogram (ECG) should be monitored more frequently as per the investigator's best medical judgment until QTc ≤480 msec.***

* In the event of QTc prolongation of >480 and ≤500 msec, possible reversible causes, such as serum electrolytes abnormalities, or usage of concomitant medications with the potential to prolong the QTc interval (see Appendix 2) should be evaluated and corrected accordingly to best clinical practice.
Abbreviations: ANC=absolute neutrophil count; AE=adverse event, QTc=corrected QT interval, ECG=electrocardiogram.

If a treatment delay results from decline in hematologic parameters, the frequency of blood count assessments should be increased as per best clinical practice.

If the re-treatment parameters are met within ≤3 weeks of dose interruption, palbociclib may be resumed as per recommended dose modification guidelines.

If the re-treatment parameters have not been met after >3 weeks of dose interruption, the patient should permanently discontinue palbociclib treatment. However, if a patient is deemed to be suitable for a lower dose of palbociclib, treatment may be resumed at a lower dose at the investigator's discretion.

5.4.3.3. Dose Reductions - Palbociclib

Following dose interruption or cycle delay, the palbociclib dose may need to be reduced when treatment is resumed. Available dose levels in case of palbociclib dose reduction are reported in Table 5.

Table 5. Available Dose Levels

Dose Level	Palbociclib	Letrozole
Starting dose	125 mg/day	2.5 mg/day
-1	100 mg/day	2.5 mg/day
-2	75 mg/day	2.5 mg/day

Palbociclib dose below 75 mg/day is not allowed.

Once a dose has been reduced, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

All dose modifications/adjustments must be clearly documented on the CRF along with reasons for dose modification/adjustment.

Palbociclib dose modifications recommended for treatment-related toxicities requiring treatment, interruption/delay, or persisting despite optimal medical treatment, are described in Table 6.

Table 6. Palbociclib Dose Modifications for Treatment Related Toxicities

Worst toxicity	Palbociclib treatment
Grade 3 neutropenia *(ANC<1000/mm^3)*	No dose adjustment is required. Consider repeating complete blood count monitoring 1 week later. Withhold initiation of next cycle until recovery to Grade ≤2, then resume at same dose level.
Grade 4 neutropenia *(ANC<500/mm^3)*	Withhold initiation of next cycle until recovery to Grade ≤2, then resume at next lower dose.
Grade ≥3 neutropenia *(ANC<1000/mm^3)* **associated with a documented infection or fever ≥38.5°C**	Withhold initiation of next cycle until recovery to Grade ≤2, then resume at next lower dose.
Grade 3 thrombocytopenia *(Platelet count<50,000/mm^3)*	No dose adjustment is required. Consider repeating complete blood count monitoring 1 week later. Withhold initiation of next cycle until recovery to Grade ≤2, then resume at same dose level.
Grade 4 thrombocytopenia *(Platelet count<25,000/mm^3)*	Withhold initiation of next cycle until recovery to Grade ≤2, then resume at next lower dose.
Grade ≥3 non-hematologic toxicity *(For nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment)*	Withhold until symptoms resolve to: • Grade ≤1; • Grade ≤2 (if not considered a safety risk for the patient). Resume at the next lower dose level.
Grade 3 QTc prolongation	Decrease 1 dose level *
Grade 4 QTc prolongation	Permanently discontinue

* Reduce the dose only if no reversible cause is identified, such as serum electrolytes abnormalities, or usage of concomitant medications with the potential to prolong the QTc interval (see Appendix 2).
Abbreviations: ANC=absolute neutrophil count; QTc=corrected QT interval.

5.5. Investigational Product Storage

The investigator, or an approved representative eg, pharmacist, will ensure that all investigational products including any marketed products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label.

Storage conditions stated in the SRSD (eg, IB) may be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be

captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the Sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct patients on the proper storage requirements for take-home investigational products.

5.6. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies.

Patients will be required to return all bottles of palbociclib at the beginning of each cycle for drug accountability (see also Section 5.2, Patient Compliance).

Drug accountability will be performed at every clinical visit prior to dispensing drug supply for the next cycle. The number of remaining capsules will be collected, documented, and recorded to assess compliance.

5.6.1. Destruction of Investigational Product Supplies

The Sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). The site will be responsible for drug destruction. If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.7. Concomitant Treatment(s)

Patients must be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with the investigator.

All concomitant medications required to clinically manage patients while they are receiving palbociclib therapy are permitted unless specified below in Section 5.7.1 and 5.7.2. Documentation of these medications will not be collected on the CRF but will need to be available from the patient's medical record upon request by the Sponsor.

An exception will be granulocyte colony stimulating factor (G-CSF). G-CSF use is permitted to treat treatment-emergent neutropenia as per current American Society of Clinical Oncology (ASCO) guidelines. Per these guidelines, if neutropenic complications are observed, secondary prophylaxis may be given at the discretion of the investigator. G-CSF use will be documented on the CRF as will other agents used to treat/manage AEs while on therapy.

5.7.1. Prohibited Medications

Anticancer agents: No additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than letrozole will be permitted during the study.

CYP3A inhibitors/inducers**:** Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, palbociclib is primarily metabolized by CYP3A4 enzymes. Coadministration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of palbociclib in humans. The concurrent use of CYP3A inhibitors/inducers listed below is not allowed in the study:

- Strong CYP3A inhibitors, including, boceprevir, clarithromycin, conivaptan, delavirdine, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, suboxone, telaprevir, telithromycin, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit.

- The following moderate CYP3A inhibitors: amprenavir, atazanavir, diltiazem, erythromycin, fosamprenavir, and verapamil.

- Strong CYP3A inducers, including carbamazepine, phenytoin, primidone, rifampin, rifapentin, and St. John's wort.

- The following moderate CYP3A inducers: felbamate, nevirapine, phenobarbital, and rifabutin.

Drugs known to cause QT interval prolongation: Refer to Appendix 2 for a list of drugs known to predispose to Torsade de Pointes.

Hormone replacement therapy: Topical estrogens (including any intravaginal preparations), megestrol acetate and selective estrogen-receptor modulators (eg, raloxifene) are prohibited during the study.

5.7.2. Medications Not Recommended

Alternative therapies should be considered whenever possible for the following treatments.

Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiologic replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.

The concurrent use of moderate CYP3A inducers such as dexamethasone or modafinil is not recommended.

The use of herbal medicines is not recommended.

6. STUDY PROCEDURES

The Schedule of Activities (Table 1) provides an overview of the protocol visits and procedures.

6.1. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or Sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

Withdrawal of consent: Patients who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him or her, or persons previously authorized by the patient to provide this information. Patients should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up: All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient. Lost to follow-up is defined by the inability to reach the patient after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the patient to 1 registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use permissible local methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the patient remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the patient's medical records.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

There are minimal protocol-specified tests and procedures for this expanded access protocol. It is the responsibility of the investigator to perform medically appropriate tests and procedures as necessary to ensure the safety and well-being of the patient.

7.1. Safety Assessments

Safety assessment will consist of monitoring of all AEs, including serious adverse events (SAEs) at every clinical visit and monitoring of hematology to be performed to check patient's eligibility at Screening, every 2 weeks (Days 1 and 14) of the first 2 cycles, then monthly on Day 1 of each subsequent cycle of treatment with palbociclib and at EOT. In the case of Grade ≥3 neutropenia, consider repeating complete blood count monitoring 1 week later in accordance with best local practice and report on the CRF in order to document the ANC value at the time of severe neutropenia as well as the time-to-recovery of neutrophils to ≥1000 cells/mm^3. Re-treatment criteria are based on time-to-recovery of neutrophil count.

For patients who develop Grade 3 or 4 neutropenia, refer to the dose modifications described in Table 6. Glycated hemoglobin (HbA1c) will be assessed at Screening, every 3 months, at EOT, and will be documented on the CRF.

Other procedures, as necessary according to standard of care and in accordance with each site's institutional guidelines, will be assessed to monitor for adverse events related to the underlying disease, treatment with palbociclib, or treatment with letrozole or supportive therapies (see Adverse Event Reporting, Section 8).

Information generated from these assessments may also be used to determine if an adverse event occurred, as defined in Section 8.3.

7.1.1. Physical Examination

A full physical examination of all major body systems will be required at Screening. Symptom-directed physical examinations will be performed as per routine clinical practice during the study. Only physical examination at Screening will be recorded on the CRF. Physical examinations performed during treatment will need to be available from the patient's medical record upon request by the Sponsor.

The Eastern Cooperative Oncology Group (ECOG) performance status scale will be required at Screening, as per routine clinical practice during the study, and at EOT. Data collected at Screening and at EOT will be recorded on the CRF. Other ECOG performance status assessments during study will need to be available from the patient's medical record upon request by the Sponsor. ECOG performance status scale is available in Appendix 1.

7.1.2. 12-Lead ECG

Three consecutive 12-lead ECGs will be performed approximately 2 minutes apart at Screening. ECG is to be repeated during the treatment, as clinically indicated. If the mean QTc is prolonged (value of >500 msec), then the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Only ECG at Screening will be recorded on the CRF. ECGs performed during treatment will need to be available from the patient's medical record upon request by the Sponsor. In the case an ECG abnormality meets the definition of AE, as determined by the investigator and according to Adverse Event Reporting (Section 8), this must be captured on an AE CRF page.

7.1.3. Laboratory Safety Assessments

Blood tests will include the following:

Hematology Panel		Metabolic Panel		Blood Chemistry Panel	
1	Absolute neutrophil count (ANC)	**1**	Glycated hemoglobin (HbA1c)	**1**	Alanine aminotransferase (ALT)
2	Platelets			**2**	Aspartate aminotransferase (AST)
3	Hemoglobin			**3**	Alkaline phosphatase
4	White blood cell (WBC) count			**4**	Sodium
				5	Potassium
				6	Total calcium
				7	Total bilirubin
				8	Blood urea nitrogen (BUN)
				9	Serum creatinine
				10	Albumin

Blood tests will be drawn at the time points described in Table 1 (Schedule of Activities), and analyzed at local laboratories.

Hematology will be performed to verify patient's eligibility at Screening, every 2 weeks (Days 1 and 14) of the first 2 cycles of therapy, then monthly on Day 1 of each subsequent cycle of treatment with palbociclib and at EOT. Hematology data will be recorded on the CRF.

In the case of Grade ≥3 neutropenia, consider repeating complete blood count monitoring 1 week later in accordance with best local practice and report on the CRF in order to document the level of neutropenia and the time-to-recovery of neutrophils to ≥1000 cells/mm^3. Re-treatment criteria are based on time-to-recovery of neutrophil count. For patients who develop Grade 3 or 4 neutropenia, refer to the dose modifications described in Table 6. The clinical actions taken as a result of Grade ≥3 neutropenia, including the use of G-CSF, if any, should be recorded.

Glycated hemoglobin (HbA1c) will be assessed at Screening, every 3 months, at EOT, and will be documented on the CRF.

Blood chemistry will be performed to verify patient's eligibility at Screening, and as per routine clinical practice thereafter. Only laboratory data at Screening will be recorded on the CRF. During the study, blood chemistry data will not be collected on the CRF but will need to be available from the patient's medical record upon request by the Sponsor.

Cycle 1/Day 1 visit: Blood chemistry and hematology are not required if acceptable screening assessment is performed within 7 days prior to randomization.

In the case any laboratory abnormality meets the definition of AE, as determined by the investigator and according to Section 8 (Adverse Event Reporting), this must be captured on an AE CRF page.

7.2. Tumor Assessments

Tumor assessments are to be performed at Screening and as per routine clinical practice and according to the patient's clinical status thereafter (Schedule of Activities, Table 1). Only the investigators' tumor assessments will be recorded on the CRF.

Tumor assessment evaluation will be conducted as per local practice at each institution.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to the investigational product(s), will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain adequate information, both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious advers event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any nonserious AE that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

AEs (serious and nonserious) should be recorded on the case report form (CRF) from the time the patient has taken at least 1 dose of investigational product through the patient's last visit.

If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the Sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see Severity Assessment, Section 8.8).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the Section 8.14.1, Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For patients with pre-existing ALT **or** AST **or** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

    Concurrent with

    - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyltransferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen (paracetamol), recreational drug, supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection, acetaminophen (paracetamol) blood levels, and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes a transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for workup of persistent pretreatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria (NCI CTC), (version 4.03 Publish Date: June 14, 2010, http://ctep.cancer.gov/reporting/ctc.html).

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Reporting Requirements, Section 8.14). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
2. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
3. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes, or is found to be, pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). Only female patients will be enrolled in this study. In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) has unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Patient Withdrawal, Section 6.1)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient or legally acceptable representative. In addition, each study patient/legally acceptable representative will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

Due to the nature of this study, the number of patients to be enrolled is not determined for the hypothesis testing. Based on the prevalence of the disease and eligible study population over the timelines of this study, it is estimated that the study will enroll 130 patients.

9.2. Efficacy Analysis

Because of the nature of the study, no inferential analyses are planned, and no hypotheses will be tested. However, some exploratory analyses may be conducted if data are available.

Specifically, analyses on objective response rate (ORR, assessed by investigator), and duration of clinical benefit may be conducted if appropriate.

Tumor assessments are to be performed at Screening and as per local practice and the patient's clinical status thereafter. No uniformed assessment schedule is planned for patients across the sites. Tumor assessments will be evaluated as per local guidelines by investigators and only their assessments will be collected on the CRF.

The ORR will be reported along with the corresponding exact 95% 2-sided confidence interval using standard methods based on the binomial distribution.

Duration of Clinical Benefit: For patients who were taking palbociclib combination treatment in the study, duration of clinical benefit is defined as the length of time patients remain on palbociclib treatment from the first day of treatment until the last day of treatment in this study.

9.3. Analysis of Other Endpoints

9.3.1. Patient Disposition

The number of patients treated and the number of patients who withdrew from the study, as well as reasons for discontinuation, will be summarized in data table format.

9.3.2. Baseline Characteristics

Demographic characteristics such as age, gender, race, prior medication, and physical examination results will be tabulated.

9.3.3. Treatment Administration

Study drug administration will be described in terms of total and median number of weeks administered, dose, and reasons for deviation from planned therapy.

9.4. Safety Analysis

Safety data will be summarized for all patients who received at least 1 dose of study medication.

9.4.1. Analysis of Adverse Events (AEs)

All AEs reported after initiation of study drug treatment will be considered as treatment-emergent AEs (TEAE). All AEs will be coded by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) coding. AE severity will be graded according to CTCAE version 4.03.

Summary tables will present the number of patients observed with TEAEs and corresponding percentages. Within each table, the AEs will be categorized by MedDRA body system and preferred term. Additional subcategories may be presented based on event severity, and/or relationship to study drug.

Individual patient listings will be prepared for all AE data.

9.4.2. Analysis of Clinical Laboratory Data

Hematology data will be recorded on the CRF at Screening and during the study as outlined in Schedule of Activities (Table 1), while blood chemistry data will be collected on the CRF only at Screening.

Data Listings will be prepared for each laboratory measurement and will be structured to permit review of the data per patient over time.

Summary tables will be prepared to display the distribution of laboratory measures over time.

Nadir ANC values and time-to-lowest ANC count, as well as time-to-recovery of ANC to $\geq$1000 cells/mm^3, will be reported on the CRF and summarized as appropriate.

9.5. Interim Analysis

No interim analysis is planned for this study. However, summaries of accumulating safety and efficacy data from the study may be presented at academic meetings during the course of the study, as appropriate.

9.6. Data Monitoring Committee

This study will not use a Data Monitoring Committee (DMC).

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the Institutional Review Board (IRB)/Ethics Committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as a source document. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the Sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient or her legally acceptable representative is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally-impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent,

spouse), and that the patient's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Patient recruitment efforts are not required for this study due to its nature of expanded access protocol.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP of which the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

The end of the trial is defined by the time of regulatory approval and commercial availability of palbociclib for the treatment of advanced breast cancer. At that time, patients enrolled in the study will be moved to commercial supply. A separate patient assistance program is designed to cover all patients (ie, "no patient left behind"). There will be some time lag between approval and commercial availability of palbociclib; therefore, there will be a 4 month or more transition period after approval to allow patients to access locally available commercial drug.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of palbociclib at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within a week of notification. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator of the results of the study based on information collected or generated by the principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-related or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

16. REFERENCES

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Appendix 1. Eastern Cooperative Oncology Group (ECOG) Performance Status

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

Appendix 2. List of Drugs Known to Predispose to Torsade de Pointes

Generic Name	Brand Name(s)
Amiodarone	Cordarone®, Pacerone®
Anagrelide	Agrylin®, Xagrid®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Cocaine	Cocaine
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Dronedarone	Multaq®
Droperidol	Inapsine®
Erythromycin	Erythrocin®, E.E.S.®
Escitalopram	Cipralex®, Lexapro®
Flecainide	Tambocor®
Halofantrine	Halfan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Levofloxacin	Levaquin®, Tavanic®
Levomethadyl	Orlaam®
Mesoridazine	Serentil®
Methadone	Dolophine®, Methadose®
Moxifloxacin	Avelox®
Ondansetron*	Zofran®
Pentamidine	Pentam®, NebuPent®
Pimozide	Orap®
Probucol	Lorelco®
Procainamide	Pronestyl®, Procan®
Quinidine	Cardioquin®, Quinaglute®
Servoflurane	Ulane®, Sojourn®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Sulpiride	Dogmatil®, Eglonyl®

Generic Name	Brand Name(s)
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

*when administered intravenously at high dose (32 mg).

Adapted from the University of Arizona Cancer Center for Education and Research on Therapeutics: "Torsades List: Drugs with a Risk of Torsades de Pointes," drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes on the University of Arizona CERT website: http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm#. This list is not meant to be considered all inclusive. See website for current list.

Appendix 3. Abbreviations

This is a list of abbreviations that may be used in the protocol.	
Abbreviation	**Term**
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BC	breast cancer
BUN	blood urea nitrogen
CDK	cyclin-dependent kinase
CDKN2A	cyclin-dependent kinase inhibitor 2A
CRF	Case Report Form
CSA	clinical study agreement
CT	CAT scan
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EOS	end of study
EOT	end of treatment
ER	estrogen receptor
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FSH	follicle-stimulating hormone
G1/S	cell cycle checkpoint/transition between G1 phase and S phase
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
HbA1c	glycated hemoglobin
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board

This is a list of abbreviations that may be used in the protocol.	
Abbreviation	**Term**
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	mitochondrial ribonucleic acid
N/A	not applicable
NCI	National Cancer Institute
PFS	progression-free survival
PgR	progesterone receptor
PT	prothrombin time
QD	quaque die (once daily)
QTc	corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SRSD	Single Reference Safety Document
SSID	single subject identification number
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
WBC	white blood cell