A PHASE 1 OPEN-LABEL PHARMACOKINETICS STUDY OF PALBOCICLIB, A CYCLIN-DEPENDENT KINASE 4 AND 6 (CDK4/6) INHIBITOR, IN POSTMENOPAUSAL CHINESE WOMEN WITH ER (+), HER2 (-) ADVANCED BREAST CANCER

Compound:	PD-0332991
Compound Name:	Palbociclib
US IND Number:	69,324
European Clinical Trial Database (EudraCT) Number:	Not Applicable
Protocol Number:	A5481019
Phase:	Phase 1

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Document History

Document	Version Date	Summary of Changes
Amendment 2	24 July 2015	1. Due to regulatory reason in China, CDK6 genotyping test is now removed from this study. Therefore, a single 4 mL blood sample Prep D1 (K_2EDTA whole blood collection optimized for DNA analysis) will not be collected pre-dose on Day -1. (Schedule of Activities/Section 3 Study Design/Section 7 Assessments) 2. Table 1 Schedule of Activities: Allowed study visit window is added in the row for Study Day. 3. Table 1 Schedule of Activities: "(only for Cycle 2)" is removed from Day 1 of Cycles ≥2 for Vital Signs and Physical Examination, since symptom-directed physical examinations, blood pressure and pulse rate will be still performed after the first two cycles. 4. Table 1 Schedule of Activities and footnote p: Clarification is added to indicate the randomization of patients into 2 groups will occur on Day -1 for different biopsy schedules in Lead-in phase and Cycle 1. 5. Table 2 Schedule of Activities: A pre-dose PK sample is added in the single dose PK part on Day 1 of Lead-in phase to meet the regulatory requirement. 6. Table 2 Schedule of Activities: Cycle number (C1) is added in the table and clarified in footnote i. Clarification is also added to footnote c to emphasize the pre-dose PK collection on Cycle 1 Day 1 is for post single dose PK sample at 120 hrs. 7. Section 1.2.1.3 Clinical Summary: Updates are added as more data become available. 8. Section 7.1 Blood Volume: Minor update is

		added. 9. Section 3 Study Design/Section 7.2.1 Tumor Assessment: Added the text about conditional acceptance for patients to continue the study treatment beyond the time of RECIST-defined disease progression. 10. Section 3 Study Design/Section 7.2.1 Tumor Assessment/Table 1 and Table 3 footnote b: Based on current imaging practice for standard of care for advanced breast cancer patient population, the frequency of post-baseline tumor assessments is changed to every 12 weeks (±7 days) from Cycle 1 Day 1. 11. Section 4.1 Inclusion Criteria: Added clarifications on definition of postmenopausal women. 12. Section 4.2 Exclusion Criteria: Commercial kit assays to test HER2 status beyond the sponsor approved ones can be also accepted for enrollment criteria, given the extremely low probability of false HER2 negative results. 13. Section 4.3 Randomization Criteria is added. 14. Section 4.4 Life Style Guidelines: Clarification is added to indicate an alcohol breath test is not required but may be conducted at the discretion of the investigator. 15. Section 5.2.2 Preparation and Dispensing: Added same requirement for letrozole as palbociclib. 16. Section 5.2.3.1 Palbociclib: If intensive PK assessments are conducted in a later cycle for any reason, the same requirement for breakfast intake is applied. 17. Section 5.2.3.1 Palbociclib: Safety evaluation (vital signs, laboratory safety and ECG) should be conducted before food intake. 18. Section 5.2.3.1 Palbociclib: Section 5.2.4.2 was

		referred for dose modification that is needed for patients experiencing investigational product related toxicity. 19. Section 5.2.6 Compliance/Section 5.3 Drug Storage and Drug Accountability: Clarification is added to require patients to return the completed patient diary. 20. Section 5.3 Drug Storage and Drug Accountability: Requirement is added to report any excursions of drug storage condition to sponsor. 21. Section 5.4.1 Prohibited Medications: Emerging data from two drug interaction studies is added in subsection for CYP3A inhibitors/inducers. 22. Section 5.4.2 Medications Not Recommended: Requirement is added to record any usage of Chinese or other herbal medicines. 23. Section 6.1 Screening: Ophthalmic procedures at screening are added for all lens grading evaluable patients (no additional procedures; only clarifications). 24. Section 6.1.1 Screen Failure is added. 25. Section 6.5 Patient Withdrawal: Clarification is added to indicate “withdrawal of consent” should not be the reason for discontinuation if a patient opts to discontinue from the active treatment phase as a result of an unacceptable adverse drug reaction. 26. Section 7.3.2 Laboratory Safety Assessments/ Table 1 Schedule of Activities footnote d: Clarification is added to indicate HgbA1c, fasting lipid panel, fasting glucose and fasting insulin will be analyzed at a central laboratory designated by the sponsor. 27. Section 7.3.2 Laboratory Safety Assessments/ Table 1 Schedule of Activities footnote d: When all of these assessments are conducted

		together, they should be done before food intake. 28. Section 7.3.3 Electrocardiogram (ECG): Heart rate should be also recorded together with other ECG measurements at the scheduled measurement time points. 29. Section 7.3.3 Electrocardiogram (ECG)/ Table 1 Schedule of Activities footnote i: ECG evaluation should be conducted before food intake. 30. Section 7.3.3 Electrocardiogram (ECG): The cutoff value of QTc prolongation and associated guidance when QTc prolongation occurs are updated. 31. Section 7.3.4.1 Visual Acuity and Refraction: In addition to Snellen notation, other methods are allowed to be used and the method being used should be indicated on the CRF pages. The original results should be recorded with the respective units indicated. Conversion to Snellen notation will not be needed. 32. Section 7.3.4.2 Intraocular Pressure Measurement: A non-contact method (Tonopen, Schiotz or Rebound tonometer) is allowed to be used for intraocular pressure (IOP) measurement. The IOP data may be pooled together for analysis. 33. Section 7.4 Pharmacokinetic Assessments: Additional clarification is added to emphasize that the dosing times both prior to and after each sample collection should be captured in the CRF pages. Two examples are also given. 34. Section 7.4 Pharmacokinetic Assessments: Requirements on administration of study drugs before and after each pre-dose PK sample are added. 35. Section 7.4.1 Plasma for Analysis of Palbociclib (PD-0332991): During the outpatient visits on Days 1, 19 and 20 in

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		Cycle 1 and Day 1 in Cycle 2, patients should be instructed to bring the drug supply and administer the drugs in the CRU after completion of PK collection on that day. 36. Section 7.5 Biomarker Assessments: Additional clarifications are added to emphasize that the collections of biomarker samples should be done as close as possible with the collection of PK samples. Sample collections for TK analysis should occur immediately after the completion of PK samplings (within 15 minutes) and skin biopsy samplings should be conducted within 30 minutes after the completion of PK samplings. 37. Section 7.5.1 Skin Biopsy: Rare contradictions and relevant precautions of skin biopsy are described. 38. Section 8 Adverse Event Reporting updated to be consistent with Pfizer template. 39. Section 9.2.1 Analysis Populations: The PK evaluable analysis set is added for PK analysis plan. 40. Section 9.2.2 Derivation of Pharmacokinetic Parameters Prior to Analysis: Summary of PK parameters will be for PK parameter analysis set and PK evaluable analysis set. 41. Section 9.4 Analysis of Other Endpoints is added. 42. Section 9.5.3 Analysis of Electrocardiogram measurements: The cutoff value of QTc prolongation is updated to be consistent with Section 7. 43. Section 15.1 Communication of Results by Pfizer was updated to be consistent with Pfizer template. 44. Appendix 7 is added for Wisconsin Age-Related Eye Disease Study (AREDS)

		2008 Clinical Lens Opacity Grading Procedure. 45. Section 16 References: More references are added for new updates. 46. Throughout the document: Editorial changes made for better readability and clarification.
Amendment 1	06 November 2014	1. Section 1 Introduction: updated the non-clinical summary, in vivo and in vitro safety pharmacology, clinical summary and safety sections with the most recent data/information available. 2. Section 1.2.3.2 Rationale for Palbociclib Dose: removed rationale for single-dose study given multiple dosing PK assessment is included in this study, and also added a clinical data summary based on the current Investigator's Brochure (2013). 3. Section 1.2.3.2 Rationale for Palbociclib Dose/Section 3 Study Design/ Section 9.1 Sample Size Determination: revised the criteria for patient replacement given that 8-12 subjects are required for PK study by China CFDA. 4. Throughout the whole document: removed "study period" to avoid any confusion since there are no different periods in this study. 5. Section 2: added biomarker analysis as another secondary objective and added biomarkers as additional secondary endpoints. 6. Section 2.2/Section 9.2: added Vz/F as one of the primary endpoints for multiple-dose PK to be consistent with that for single-dose PK assessment; revised PK parameter table per request from Pfizer PK analyst for this study. 7. Section 2.2: added 1-year PFS probability as another secondary efficacy endpoints. 8. Schedule of Activities/Section 3 Study Design: changed to keep patients in the clinical unit for

		at least 72 hours after palbociclib dosing for both single- and multiple-dose PK assessments to reduce the number of outpatient visits to improve the compliance with study conduct. 9. Section 3 Study Design: added two paragraphs to discuss the rationale for biomarker assessments and pharmacogenomic analyses, respectively. 10. Schedule of Activities/throughout the whole document: updated the study day numbers to avoid any confusion between Lead-in phase (Day 1 to Day 5) and Cycles ≥1 (Days ≥1) activities. The day number for pre-dose procedures and admission of patients to clinical unit was changed to Day -1. 11. Schedule of Activities/Section 4.3.2 and 5.2.3.1: removed fasting requirement from palbociclib dosing instructions, and added requirement that palbociclib should now be taken with meals. On days with intensive PK collections (only Day 1 in Lead-in phase and Day 21 in Cycle 1), the content requirement of provided breakfasts was added. 12. Schedule of Activities/Section 7.3.2: added more laboratory tests in the blood chemistry panel (hemoglobin A1c, fasting glucose, fasting insulin and fasting lipid panel) to evaluate whether or not palbociclib affects glucose metabolism. 13. Schedule of Activities: removed several PK sample collections. 14. Schedule of Activities: increased the frequency of hematology assessments. The schedule of hematology assessments in Lead-in phase and Cycle 1 was moved to Table 2 for clarification. 15. Schedule of Activities/Section 7.3.3: updated ECG evaluation schedule and added procedure requirement in Table 1 and removed the ECG part from Table 2.

		16. Schedule of Activities/Section 7.3.4: added ophthalmic procedures for all evaluable patients to assess the potential risk of palbociclib-associated crystalline lens changes. 17. Schedule of Activities/Section 7.4: added requirement for steady state PK sample collection (without dosing interruption for at least 8 days prior to sample collection). 18. Schedule of Activities/Section 7.4.1: added clarification on deviation from required collection time for PK samples and instructions for collection of pre-dose PK samples; added instructions regarding drug administration to ensure the collection of pre-dose PK samples. 19. Schedule of Activities/Section 7.4.1: the blood volume collected for each PK sample was reduced to 2 mL from 3 mL. 20. Schedule of Activities/ Section 7.5: added separate blood sample for pharmacogenomic analysis (CDK6 polymorphism [SNP rs445]). 21. Schedule of Activities/Section 7.6: added skin punch biopsy procedure and blood test for biomarker assessments. The detailed time points were described in Table 2. 22. Schedule of Activities: removed urine drug test and alcohol breath test because these tests are inappropriate in a study in cancer patients. 23. Schedule of Activities: added clarification that some pre-dose procedures will not be required on Day -1 if already performed with acceptable results within 7 days prior to Day -1. 24. Section 5.2.1 Formulation and Packaging: updated medication information for letrozole to indicate that it will be sourced locally at China sites. 25. Section 5.2.2: added more detailed instruction for drug preparation/dispensing.

		26. Section 5.2.3.2: added clarification that letrozole will be administered alone from Day 2 to 5 in Lead-in phase, during the palbociclib off-treatment week in every cycle, and in the event of palbociclib dosing interruption. 27. Section 5.2.4.2.2. Dose Delay (for palbociclib)/Section 6.3. Active Treatment Phase: added one paragraph to clarify the procedures required on Day 1 of a new cycle when the start of a new cycle is delayed due to treatment-related toxicity. 28. Section 5.2.4.2.3. Dose Reductions: added Table 7 to clarify the recommended palbociclib dose modification for hematologic toxicities by CTCAE grade and treatment day. This table was added in agreement with the palbociclib Risk Management Committee's revision of the blood counts monitoring plan. 29. Section 5.4.1. Prohibited Medications: emphasize that CYP3A inhibitor/inducers should be prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first PK sample until the completion of all required PK samplings; editorial changes to differentiate between strong and moderate CYP3A inducers/inhibitors. 30. Section 5.4.1. Prohibited Medications: added prohibition of taking proton-pump inhibitor (PPI). According to new available data from a drug interaction study, the total palbociclib exposure (AUC_{inf}) was reduced only by approximately 13% under fed conditions when coadministered with PPI. Therefore, PPIs will be prohibited only for PK assessments (from at least 10 days before the collection of the first PK sample until the completion of all the required PK samplings). 31. Section 5.4.3. Permitted Medications: added recommendation to use local antacids as well as H_2-receptor antagonists as alternative treatments for patients requiring

		gastroprotective treatment. Staggered dosing regimens will be required only on PK sampling days. Dosing of palbociclib should occur at least 10 hours after H_2-receptor antagonists evening dose and 2 hours before the H_2-receptor antagonists morning dose. Local antacids should be given at least 2 hours before or 2 hours after administration of palbociclib. 32. Section 5.4.3. Permitted Medications: added clarification for allowing acid reducing agents to be used after the completion of PK evaluations. 33. Section 5.4.2. Medications Not Recommended: removed coadministration of CYP3A substrates with palbociclib from Section 5.4.2 based on new available data that showed palbociclib is a weak CYP3A inhibitor. 34. Section 6.5: added clarifications on patient withdrawal. 35. Section 7.1: updated blood volume section and Table 9 to only provide the estimation of blood amount during the Lead-in phase and Cycle 1 where the amount of collected blood will be much larger than other cycles. The total blood sampling volume during the whole study cannot be estimated because the trial duration is determined by disease progression, unacceptable toxicity, withdrawal of consent, or patient death. 36. Section 8. Adverse Event Reporting: made changes to comply with the current version of protocol template. 37. Section 9.2.1. Analysis Populations: made changes on the definitions of PK concentration population and PK parameter analysis population to be consistent with the PK design. 38. Section 9.2.2. Derivation of Pharmacokinetic Parameters Prior to Analysis: made changes to avoid any confusion.

		39. Section 9.3. Efficacy Analysis: added definition of efficacy analysis set; added description about censoring progression-free survival and duration of response; added descriptions for calculating the 1-year PFS probability. 40. Section 9.4. Safety Analysis: changed the instruction to include the medical history, physical examination of patients into the study database; added screening values of laboratory data, ECGs, and vital signs into the study database as baseline levels. 41. Section 9.4.2: added brief description of analysis for ocular events. 42. Section 9.4.3: added clarifications and removed repeated paragraphs about ECG analysis. 43. Section 10/Section 11: removed PCRU-related parts given that the study will be conducted at external sites in China. 44. Section 15: made changes to comply with the current version of protocol template. 45. Section 16: added more references to support the included data and information. 46. Editorial changes made to correct typos and formatting issues.
Original Protocol	10 APR 2013	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc

Table 1. SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS 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 wellbeing of the subject.

Protocol Activity	**Screening (≤28 days prior to study entry)**		**Single-Dose PK (Lead-in phase Days 1-5)**	**Mutiple Dose PK (Cycle 1)**			**Cycles ≥2**			**End of Treatment /Withdrawal (EOT)[r]**	**Follow -up**
Study Day		**Day -1[a]** From Day -4 to Day -1	**Days 1~5** From Day -3 to Day 1	**Day 1**	**Day 14**	**Day 21**	**Day 1** (±2d, only for cycle >2)	**Day 14** (±2d)	**Day 21** (±2d)	±7	
Baseline Documentation											
Informed Consent	X										
Medical/Oncology History	X	X									
Baseline Signs/Symptoms[b]	X	X									
Vital Signs and Physical Examination[c]	X	X		X			X			X	
ECOG Performance Status	X			X			X			X	
Laboratory Tests											
Hematology[d]	X	X	See Table 2 for detailed time points				X		X (only for Cycle 2)	X	
Blood Chemistry[d]	X	X		X	X		X	X (only for Cycle 2)		X	
HgbA1c[d]		X	Cycle 4 Day 1 and every 3 months thereafter							X	
Fasting Glucose and Fasting Insulin[d]		X				X	X (only for Cycle 2)			X	
Fasting Lipid Panel[d]		X								X	
Urinalysis[e]	X	X								X	
Coagulation[f]	X	X								X	

Protocol Activity	**Screening (≤28 days prior to study entry)**		**Single-Dose PK (Lead-in phase Days 1-5)**	**Mutiple Dose PK (Cycle 1)**			**Cycles ≥2**			**End of Treatment /Withdrawal (EOT)[r]**	**Follow -up**
Study Day		**Day -1[a]** From Day -4 to Day -1	**Days 1~5** From Day -3 to Day 1	**Day 1**	**Day 14**	**Day 21**	**Day 1** (±2d, only for cycle >2)	**Day 14** (±2d)	**Day 21** (±2d)	±7	
HbsAg, anti- HCV[g]	X										
HIV test[h]	X										
ECG (in triplicate)[i]	X	X		X	X		X	X (only for Cycle 2)		X	
Ocular Assessment[j]	X						See footnote for details			X	
Study Treatment											
Letrozole			Once daily continuously (from Lead-in phase Day 1)								
Palbociclib[k]			X (Only Day 1)	Once daily on Day 1 to Day 21 of each cycle followed by 7 days off							
Disease Assessments[l]											
CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; Clinical evaluation of superficial disease	X						Performed every 12 weeks (±7 days) from C1D1			X	
Radionuclide Bone Scan, Whole Body	X						Performed every 24 weeks (± 7 days) from C1D1			X	
Other Clinical Assessments											
Drug Compliance[m]				X			X				
Adverse Event Reporting[n]	X	X	Assessed throughout the study							X	X
Concomitant Medications/ Treatments[o]	X	X	Assessed throughout the study							X	X
Pharmacokinetic Blood Sampling			See Table 2 for detailed time points								
Skin Biopsy[p]		X	See Table 2 for detailed time points								

Protocol Activity	**Screening (≤28 days prior to study entry)**		**Single-Dose PK (Lead-in phase Days 1-5)**	**Mutiple Dose PK (Cycle 1)**			**Cycles ≥2**			**End of Treatment /Withdrawal (EOT)[r]**	**Follow -up**
Study Day		**Day -1[a]** From Day -4 to Day -1	**Days 1~5** From Day -3 to Day 1	**Day 1**	**Day 14**	**Day 21**	**Day 1** (±2d, only for cycle >2)	**Day 14** (±2d)	**Day 21** (±2d)	±7	
Randomization[p]		X									
Thymidine Kinase Blood Test [q]		X	See Table 2 for detailed time points								

a. **Day -1:** Patients will be admitted to the Clinical Research Unit (CRU) on Day -1 and will be required to stay in the unit until at least 72 hours (on Day 4) following single dose of palbociclib based on the availability of CRU. In the case that screening and Day -1 occur on the same day, procedures scheduled on Day -1 do not need to be repeated.
b. **Baseline Signs/Symptoms:** Baseline tumor related signs and symptoms will be recorded at the screening and Day -1 visit prior to dosing and then reported as adverse events during the trial if they worsen in severity or increase in frequency.
c. **Vital Signs and Physical Examination:** A full physical examination including an examination of all major body systems, height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider, will be required at screening, Day -1, Day 1 of Cycles 1 and 2 as well as the end of treatment (EOT). Physical examinations will not be required on Day -1 if an acceptable screening examination is performed within 7 days prior to Day -1. Symptom-directed physical examinations, blood pressure and pulse rate will be performed at subsequent visits.
d. **Hematology, and Blood Chemistry Panel:** Hematology includes hemoglobin (Hb), WBC, absolute neutrophils, platelet count and the assessments will be conducted regardless of food intake. Blood chemistry includes AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, BUN (or urea), serum creatinine, albumin, hemoglobin A1c (HgbA1c), fasting glucose, fasting insulin, and fasting lipid panel. HgbA1c assessments will be conducted regardless of food intake; fasting glucose, fasting insulin and fasting lipid panel will be assessed following an overnight fast (at least 10 hours); samples for other blood chemisty tests should be collected following at least a 4-hour fast. Therefore, if all of these assessments are conducted together, they should be done before food intake. The hematology and blood chemistry assessment schedules should be referred to in Table 1 and Table 2. Additional hematology/chemistry panels may be performed as clinically indicated. HgbA1c, fasting lipid panel, fasting glucose and fasting insulin will be shipped to a central laboratory designated by the Sponsor for analysis.
e. **Urinalysis:** Urine protein and blood. Dipstick is acceptable. If positive, microscopic analysis will be performed and 24-hr urine samples will be collected (only for protein excretion). This assessment will not be required on Day -1 if an acceptable screening assessment is performed within 7 days prior to Day -1.
f. **Coagulation:** PT or INR, PTT or aPTT. Additional coagulation studies may be performed as clinically indicated. The assessment will not be required on Day -1 if an acceptable screening assessment is performed within 7 days prior to Day -1.
g. **HbsAg, anti-HCV:** Hepatitis B surface antigen (Hbs Ag) and antibody against hepatitis C virus (anti-HCV) tests.
h. **HIV test:** Human Immunodeficiency Virus test.

i. **ECG:** At each scheduled ECG evaluation, 3 consecutive 12-lead pre-dose ECGs will be performed approximately 2 minutes apart to determine the mean QTc interval. All the assessments will be made after at least a 10-minute rest in a supine position. If ECG and PK collections are scheduled on the same day (Cycle 2 Day 1), pre-dose ECG assessments should occur before PK collections. All ECG evaluations should be conducted before food intake.
j. **Ocular Assessment**: Ocular assessments should be conducted at screening and on study treatment after 3 months (Cycle 4 Day 1), 6 months (Cycle 7 Day 1), 12 months (Cycle 13 Day 1), every 12 months (Day 1 of Cycles 25, 37 etc.) thereafter, as well as at the EOT. Additional ocular assessments may be performed during the study as clinically indicated . The ocular assessments will include: best corrected distant visual acuity, refractive error associated with best corrected distant visual acuity, intraocular pressure (IOP – one reading), slit-lamp biomicroscopy of the anterior segment including cell count and flare grading, crystalline lens grading using the Wisconsin Age-Related Eye Disease Study (AREDS), 2008 Clinical Lens Opacity Grading procedure, and fundoscopy. All ocular assessments will be performed by ophthalmologists.
k. **Study Treatment Administration:** Palbociclib and letrozole should be administered together with food. On Day 1 in Lead-in phase and Day 21 in Cycle 1(intensive PK sampling days), similar breakfast will be provided to patients approximately 30 minutes prior to the administration of palbociclib (breakfast started at approximately 0930 AM). Breakfast will be consumed within a 20-minute period with study drugs administered approximately 10 minutes after completion of the meal. At least 80% of the provided breakfast should be consumed prior to palbociclib administration. The provided breakfast should be moderate-fat standard-calorie meal (approximately 15% protein, 50% carbohydrate, 35% fat diet for a total of 500-700 calories).
l. **Disease Assessments:** Refer to the tumor assessment requirement flowchart (Table 3) for details and timing of procedures.
m. **Drug Compliance:** Patients will be required to return the completed patient dosing diary and all bottles of palbociclib and letrozole including any unused capsules/tablets to the clinic for drug accountability at the beginning of each cycle. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle.
n. **Adverse Events:** For SAEs, the active reporting period begins from the time that the patient provides informed consent through and including 28 calendar days after the last administration of the investigational product. Serious adverse events 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 serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor. AEs (serious and non serious) should be recorded from the time the patient has taken at least one dose of study treatment through last patient visit.
o. **Concomitant Medications/Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days after the last dose of study treatment. No Chinese or other herbal medicines will be allowed during PK portion. No Chinese anti-cancer herbal medicines will be allowed after the PK portion (Cycle 1). The use of herbal medicines is not recommded from Cycle 2. Any usage of Chinese or other herbal medicine should be recorded.
p. **Skin Biopsy:** Skin tissue samples are required to be collected from enrolled patients at pre-dose on Day -1. On Day -1, patients will be randomized into 2 groups for different collection schedules in Lead-in phase and Cycle 1. Refer to Table 2 for timing details of post-dose procedures.
q. **Thymidine Kinase Blood Test:** Blood samples will be collected for analysis of thymidine kinase (TK) activity at pre-dose on Day -1. Refer to Table 2 for timing details of post-dose procedures.
r. **End of Treatment/Withdrawal**: Obtain these assessments if not completed during the previous 4 weeks (or within the previous 8 weeks for disease assessments).

Table 2. Blood Sampling Time Points for PK, Hematology and Biomarker Evaluations During Single-Dose and Multiple-Dose PK Portion

Single- or Multiple-Dose PK[a]	Single-Dose PK (Lead-in phase)										C1[i]	Multiple-Dose PK in Cycle 1[f]														Cycle 2
Study Day	**1**						**2**	**3**	**4**	**5**	**1**	**14**	**19**	**20**	**21**						**22**	**23**	**24**	**25**	**26**	**1**
Hour post dose	0[b]	2	4	6	8	10	24	48	72	96	120[b,c]	0	0[b]	0[b]	0[b]	2	4	6	8	10	24	48	72	96	120	0[b]
PK blood collection for pabociclib[d]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
PK blood collection for letrozole[d]													X	X	X											X
Hematology[e]									X		X	X			X								X			X
Skin Biopsy[g]						X	X													X	X	X	X	X	X	
Blood Samples for TK test[h]			X		X	X	X		X		X						X		X	X	X	X	X	X	X	X
Confinement	→	→	→	→	→	→	→	→	X					X	→	→	→	→	→	→	→	→	X			
Discharge from CRU									X														X			
Outpatient Visit										X	X	X	X											X	X	X

a. For both single-dose and multiple-dose PK collections, patients will be required to stay in the CRU for at least 72 hours following palbociclib dosing based on the availability of CRU, and come back for outpatient visits to provide PK samples as scheduled. For PK collections scheduled before 24 hours post-dose in CRU, deviation of required collection time within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) from dosing will not be captured as a protocol deviation, as long as the actual collection time is recorded. For samples scheduled after 24 hours post-dose, collections obtained within 10% of the sampling interval (ie, 24 hours in this study) will not be captured as a protocol deviation as long as the actual collection time is recorded. For the PK

samples collected during outpatient visits, deviation of required collection time larger than 10% of sampling interval (ie, 24 hours in this study) may be acceptable as long as the actual collection time is recorded.

b. Pre-dose PK samples should be taken immediately prior to any palbociclib and letrozole morning dosing on that day (within approximately 15 minutes prior to the dosing). On these days, administration of palbociclib and letrozole should occur in the CRU to ensure the pre-dose PK samples can be collected; on Days 1, 19 and 20 in Cycle 1 and Day 1 in Cycle 2, patients should be instructed to bring the drug supply and administer the drugs in the CRU after completion of PK collection on that day.
c. On Cycle 1 Day 1, the post single dose PK sample at 120 hrs will be taken prior to dosing.
d. 2 mL of whole blood will be drawn into a tube containing K_2EDTA for each time point.
e. Hematology assessments will be evaluated at screening and/or Day -1, on Day 4 before discharge in Lead-in phase, on Cycle 1 Day 1 before dosing of palbociclib, on Cycle 1 Day 14, 21, 24 in Cycle 1, on Cycle 2 Day 1 and 21 as well as Day 1 in Cycles ≥3. On Day 1 of each cycle (at least for 4 subsequent cycles after the first 2 cycles), the assessments should be conducted before dosing to ensure the tolerability of patients. Actual time of assessments must be documented. Once complete blood count has stabilized, further monitoring should be conducted as clinically indicated.
f. PK sample collections scheduled after multiple dosing of palbociclib should be conducted given that there is no dosing interruption for at least 8 days prior to sample collection. If the sample collection is missed for any reason, or if the PK data collected are deemed not evaluable by the Sponsor, then the PK sample collection may be repeated during a later cycle.
g. Skin biopsy for biomarker assessments will be conducted. Samples will be collected from all enrolled patients at pre-dose on Day -1. In Lead-in phase and Cycle 1, patients will be randomized into 2 groups for different collection schedules: patients from Group 1 will be required to provide samples on Day 2 (24 hours post dose) in Lead-in phase, Days 22, 24 and 26 in Cycle 1; patients from Group 2 will be required to provide samples on Day 1 (10 hours post dose) in Lead-in phase, Days 21 (10 hours post-dose), 23 and 25 in Cycle 1. The biomarker sample collection should be conducted together with PK collection, and the actual collection time must be documented.
h. 3 mL of whole blood will be drawn into a tube at each scheduled time point right after collection of PK samples (no need to perform venipuncture again at the same time point). Actual collection time should be recorded.
i. C1 represent Cycle 1.

NOTE:

During the periods of intensive PK blood draws, an indwelling catheter is allowed if there is a need.

Table 3. Tumor Assessment Requirements Flow Chart

	Screening[a]	Treatment Period[b]	End of Treatment Visit[c]
CT[d] or MRI of chest, abdomen, and pelvis (CAP)	Required[e]	Required	Required
CT[d] or MRI of any other site of disease, as clinically indicated	Required[e,f]	Required for sites of disease identified at screening	Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere
Radionuclide bone scan (whole body) and correlative bone imaging	Required[g,h]	Required for sites of disease identified at screening or if clinically indicated[i]	Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere
Photographs of all superficial lesions as applicable[j]	Required	Required for sites of disease identified at screening	Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere

a. Screening scans must occur within 4 weeks (ie, 28 days) prior to study entry unless otherwise specified.
b. Tumor assessment must be done during the treatment period, every 12 weeks(±7 days) from C1D1, bone scans (as applicable) every 24 weeks (±7 days) from C1D1 until radiographically and/or clinically (ie,for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow up), whichever occurs first. The schedule of assessments should be fixed according to the calendar, regardless of treatment delays/interruptions. Imaging assessments are to be scheduled using the C1D1 date as the reference date for all time-points and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted. The same tumor assessment technique MUST be used throughout the study for a given lesion/patient.
c. Patients who have already demonstrated objective disease progression as per RECIST v.1.1 do not need to have scans repeated at the end of treatment visit.
d. The CT scans, including brain CT scan if applicable, should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it must be performed a few days before any treatment that may affect bone-marrow cellularity (eg, G-CSF).
e. Radiographic assessments obtained per the patient's standard of care prior to study entry do not need to be repeated and are acceptable to use as baseline evaluations, if (1) obtained within 28 days before study entry, (2) they were performed using the method requirements outlined in RECIST v.1.1 (3) the same

technique/modality should be used to follow identified lesions throughout the trial for a given patient, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.

f. Baseline brain scans are only required if signs and symptoms suggest presence of metastatic brain disease. Brain scans performed before the signing of informed consent as routine procedures (but within 6 weeks before study entry) do not need to be repeated and may be used as baseline assessments as long as (1) tests were performed using the method requirements outlined in RECIST v.1.1 (2) the same technique/modality should be used to follow identified lesions throughout the trial for a given patient (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. Post-baseline repeat brain scans will only be required only if metastases are suspected.

g. Bone scans will be carried out at baseline for all patients within 12 weeks prior to study entry in order to detect bony sites of disease. Bone scans performed before the signing of informed consent as routine procedures (but within 12 weeks before study entry) do not need to be repeated and may be used as baseline assessments as long as (1) tests were performed using the method requirements outlined in RECIST v.1.1 (2) the same technique/modality should be used to follow identified lesions throughout the trial for a given patient (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.

h. Any suspicious abnormalities (ie, hotspots) identified on the bone scans at baseline and on subsequent bone scans MUST be confirmed by X-ray, CT scan with bone windows or MRI. The same modality must be used throughout the trial for confirmation for a given lesion/patient. Bone lesions identified at baseline will be followed up according to the same assessment schedule (ie, every 12 weeks ±7 days from C1D1) as for all other lesions. Areas that have received palliative radiotherapy cannot be used to assess response to study treatment.

i. If bone lesions were identified at baseline, then bone scans will be repeated during the active treatment phase every 24 week (±7 days) from the date of C1D1 and at the time of confirmation of CR. If no bone lesions were identified at baseline, then bone scans will only be repeated during the active treatment phase when clinically indicated (ie, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) but are required at the time of confirmation of CR. New Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan with bone windows or MRI.

j. Clinical assessment of superficial disease must be carried out on the same date as the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the case report form (CRF).

Notes:

- Radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression at the discretion of the investigator. If progressive disease is confirmed per RECIST v.1.1, patients are expected to discontinue study therapy. However, patients may continue treatment as assigned beyond the time of RECIST-defined PD at the discretion of the investigator if that is considered to be in the best interest of the patient and as long as no new anticancer treatment is initiated.

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APPENDICES

1. INTRODUCTION

1.1. Indication

Estrogen receptor-positive (ER(+)), HER2-negative (HER2(-)) Advanced Breast Cancer (ABC) in Chinese patients who have not received any prior systemic anti-cancer therapy for their advanced disease

1.2. Background and Rationale

Breast Cancer is the most common invasive cancer in women, with more than 1.3 million cases and over 450,000 deaths occurring worldwide annually. In China, the incidence of breast cancer is 21.6 per 100,000 individuals, the mortality rate is 5.7 per 100,000 individuals.[1] Although age-adjusted mortality from breast cancer has been decreasing since 1990, the median survival for patients with metastatic disease is still only approximately 18 to 24 months[2] and the medical need for more active agents in this clinical setting remains very high.

Palbociclib, an orally active pyridopyrimidine, is a potent and highly selective reversible inhibitor of cyclin-dependent kinase (CDK)4 and CDK6. The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated in laboratory models and early clinical trials. Palbociclib preclinical data indicate that it may be expected to have direct effect on growth arrest as well as potential secondary cytoreductive activity. Treatment of cultured tumor cells (MDA-MB-435 breast cancer cell line and Colo-205 colon cancer cell line) 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.

The only known natural substrate for CDK4/6 kinase activity is the retinoblastoma (Rb) protein. In a small portion of tumors (eg, retinoblastoma, small-cell lung cancer), control of G_1/S progression is lost by Rb gene mutation.[3, 4, 5] In more common tumors, however, other genetic and epigenetic changes lead to increases in CDK4/6 activity which contributes to tumor cell growth. Thus, tumor cell proliferation in these tumors may be particularly sensitive to selective inhibitors of CDK4/6.

The role of estrogens in breast cancer etiology and progression is well established. Modification of estrogen activity or synthesis represents the treatment of choice for postmenopausal women with hormonal receptor positive advanced breast cancer, particularly for those with slowly progressive disease and limited tumor-related symptoms. Letrozole is an oral nonsteroidal aromatase inhibitor and it is approved worldwide for the first-line treatment of postmenopausal women with hormone receptor-positive advanced breast cancer (ABC).

As mentioned, palbociclib prevents cell cycle progression from G1 to S phase and has shown antitumor activity in multiple preclinical models, including in estrogen receptor-positive (ER+) luminal breast cancer cell lines.

Furthermore, pre-clinical exploration using a breast cancer cell line panel has demonstrated presence of retinoblastoma (Rb) protein and upregulation of cyclin D1 as well as decreased CDKN2A (p16) that were 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 interaction of estrogens and CDKs and the important role of cell cycle-related proteins in the genesis and maintenance of breast cancer, support to the clinical development of palbociclib in combination with an aromatase inhibitor (AI) like letrozole in the first-line treatment of ER(+)/HER2(-) ABC patients.

1.2.1. Overview of Palbociclib

Oral palbociclib is a highly selective, reversible inhibitor of CDK 4 and 6. Inhibition of CDK 4/6 blocks DNA synthesis by prohibiting progression of the cell cycle from G1 to S phase. Data from nonclinical studies indicate that palbociclib may have cytoreductive as well as cytostatic effects.

1.2.1.1. Non-Clinical Pharmacokinetic and Metabolism of Palbociclib

In nonclinical species (rat, dog, and monkey), palbociclib exhibits low to moderate plasma clearance, large volume of distribution, and moderate oral bioavailability ranging from 23% to 56%.

Plasma protein binding of palbociclib is moderate in mouse, rat, dog, and human plasma. Plasma protein binding was not found to be saturable over the tested concentration range of 0.5 to 5.0 μg/mL. Mean fraction unbound (fu) in human plasma ranged from 0.137 to 0.161. Palbociclib shows a modest preferential distribution to red blood cells (RBCs) over plasma in humans with a concentration ratio of blood/plasma of 1.63, but similar distribution between red blood cells and plasma in nonclinical species.

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 sulfotransferase (SULT) 2A1 and CYP3A enzymes. One of primary metabolites observed in in vitro and animal systems is an active lactam metabolite designated PF-05089326.

In vitro, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations and thus, showed low potential for CYP-mediated pharmacokinetic drug interactions. However, palbociclib and PF-05089326 caused time-dependent inhibition of CYP3A midazolam 1'-hydroxylase and testosterone 6β-hydroxylase activities with K_i and k_{inact} values for palbociclib of 10 μM, 0.036 min^{-1} and 19 μM, 0.087 min^{-1} and for PF-05089326 of 7.0 μM, 0.094 min^{-1} and 6.4 μM, 0.15 min^{-1}, respectively. Therefore, palbociclib and its metabolite may have the potential for pharmacokinetic drug interactions with compounds for which CYP3A-mediated metabolism constitutes the primary mechanism of clearance.

Experiments in Madin-Darby canine kidney (MDCK) cells transfected with P-glycoprotein (P-gp) or breast cancer resistant protein (BCRP) indicated that palbociclib was a moderate substrate for both. The efflux of palbociclib was found to be concentration dependent and

appeared to be saturable with efflux ratios less than 2 when palbociclib concentrations were greater than 0.52 and 1.96 μM for P-gp and BCRP, respectively. Palbociclib inhibited P-gp and BCRP in MDCKII-multiple drug resistance (MDR)1 and MDCKII-BCRP cells with a 50% inhibitory concentration (IC50) of >32 μM (>~14.3 μg/mL), indicating a low potential for palbociclib to inhibit these transporters at clinically relevant concentrations. In vitro, palbociclib, at concentrations up to ~32 μM, did not inhibit organic cation transporter (OCT)-2, organic anion transporters (OAT)-1 and 3, organic anion transporting polypeptide (OATP)-1B1 and 1B3, and bile-salt export pump (BSEP).

Hepatic uptake and biliary excretion of palbociclib was investigated in vitro using a sandwich culture human hepatocyte model in the presence and absence of rifamycin SV and divalent cations. Palbociclib showed high passive permeability to human hepatocytes and transporter-mediated uptake was observed at about 15% of the total uptake into hepatocytes. Biliary excretion of palbociclib was considered minimal as accumulation in presence and absence of divalent cations was similar. Palbociclib accumulation in the presence and absence of rifamycin SV were similar indicating a minor role, if any, for OATP1B1 and OATP1B3 in palbociclib transport.

1.2.1.2. In Vivo and In Vitro Safety Pharmacology of Palbociclib

In preclinical studies, palbociclib caused decreases in heart rate (HR; up to 8 beats per minute [bpm]) that corresponded with increases in respiratory rate (RR) interval (up to 73 milliseconds [msec]) and increases in systolic blood pressure (up to 6 mmHg) in dogs given a single oral dose of 10 and 30 mg/kg between 4.5 and 20 hours postdose (140 ng/mL unbound). In addition, increases in the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle (QT; up to 14 msec) and heart rate corrected QT (QTc; up to 9 msec) interval were identified in the dog at ≥3 mg/kg with a threshold concentration of 67 ng/mL (unbound) resulting in a 3.7-fold above human clinical exposure at 125 mg once a day (QD). Palbociclib inhibited hERG current in human embryonic kidney 293 (HEK293) cells with an observed IC_{50} of 3.2 μM (1432 ng/mL). In the Purkinje fiber assay palbociclib had no effect on the resting membrane potential, action potential amplitude, V_{max}, and action potential duration at 50% repolarization (APD_{50}) at 0.1 and 1 μM; however, a statistically significant 8.2% increase in action potential duration at 90% repolarization (APD_{90}) occurred at 10 μM (4475 ng/mL). In the hERG assay with the oxidative metabolite of palbociclib, PF-05089326, the IC_{50} was not achieved at 10 μM that was the maximum concentration tested due to the compound solubility limit.

In repeat-dose rat and dog toxicity studies of up to 15 weeks in duration, the primary palbociclib-related toxicities were observed in the bone marrow, lymphoid tissues, and testes. Decreased cellularity in the bone marrow and lymphoid tissues, and increased iron pigment in the bone marrow, liver, and spleen were associated with the presence of hematological changes that included decreases in red blood cell parameters and leukocytes. Partial to complete reversibility of these toxicities was demonstrated following a 4 week recovery period, with the exception of the testicular and epididymal changes for which reversal was not observed in the dog. These toxicities occurred in both rats and dogs, and are consistent with the intended pharmacologic effect of palbociclib (ie, cell cycle inhibition).[6,7,8]

In an ongoing 27-week repeat-dose rat toxicity study, cataracts were identified in male rats at ≥30 mg/kg/day and correlated microscopically with lens degeneration. Although cataracts were not identified from ophthalmic evaluations at 10 mg/kg/day in males or at any dose in females, lens degeneration was noted microscopically in male rats at ≥10 mg/kg/day (750 ng·hr/mL, unbound) and in female rats at 50 and 100 mg/kg/day (331 ng·hr/mL, unbound). These microscopic effects were seen at exposures that are comparable to clinical exposure at the recommended human dose of 125 mg QD.

The mechanism for cataract formation in palbociclib-treated rats is unknown; however, emergent data from the 27-week rat toxicity study suggests its pathogenesis may be related to altered glucose metabolism. Ten of 11 male rats with lens degeneration were shown to have glycosuria (+2 or +3) and/or increased serum glucose (compared to the upper range of control values) (unscheduled deaths not included due to the lack of clinical chemistry data). One of 3 female rats with lens degeneration also had glycosuria and hyperglycemia. In addition to the correlation observed between altered glucose metabolism and lens degeneration, a correlation between altered glucose metabolism and pancreatic islet cell vauolation was identified in all (10 of 10) male animals with the histological change. In females, the one female with lens degeneration that correlated with glycosuria and hyperglycemia also had pancreatic islet cell vacuolation.

Maternal and fetal effects were observed in embryofetal development studies conducted in the rat and rabbit with palbociclib. Maternal body weight gain and food intake were reduced at 300 and 20 mg/kg/day in pregnant rats and rabbits, respectively. Reduced fetal body weights (95% of control) were identified in rats only at 300 mg/kg/day. A low incidence of small phalanges on the forepaws were noted (3 fetuses from 2 litters; skeletal variation) at 20 mg/kg/day in rabbits.

The genotoxic potential of palbociclib was assessed in a battery of *in vitro* and *in vivo* tests. Palbociclib tested negative in the microbial reverse mutation assay when tested up to 5 mg/plate in the presence and absence of exogenous metabolic activation. However, palbociclib tested positive in an exploratory *in vitro* micronucleus assay when tested in a 24-hour test. In a subsequent *in vitro* micronucleus test, kinetochore-staining was used to discriminate micronuclei induced by chromosomal breakage from those induced by chromosomal loss. The results from this study show that palbociclib induces predominantly micronuclei containing whole chromosomes and is therefore considered aneugenic in the *in vitro* test system. The lack of clastogenic potential was further confirmed in the human lymphocyte aberration assay when tested in 3- and 24-hour tests without metabolic activation, and in a 3-hour test with metabolic activation up to concentrations limited by cytotoxicity. Palbociclib was also tested in an *in vivo* bone marrow micronucleus assay in rats at up to maximally tolerated doses of 50, 100 and 200 mg/kg in males and 100, 200, 400 mg/kg in females following once daily oral dosing for 3 weeks. Palbociclib induced micronuclei in the polychromatic bone marrow erythrocytes of male rats at 100 and 200 mg/kg but not at 50 mg/kg or in female rats when tested up to maximally tolerated doses. Systemic Day 21 area under the plasma concentration versus time curve (AUC) exposure at the no-observed effect levels (NOEL) of 50 mg/kg in males and 400 mg/kg in females was 17300 and 11100 ng•hr/mL, respectively. Based on the lack of direct DNA interaction and

the expected safety margin for aneugenic activity, there are no perceived genetic toxicity risks to humans at doses up to 125 mg QD allowing for dosing in healthy volunteers.

Complete information on the preclinical toxicology of palbociclib can be found in the Investigator's Brochure.

1.2.1.3. Clinical Summary

As of December 2014, the clinical program with palbociclib included 7 studies in advanced cancer patients. Two Phase 1 and 1 Phase 1/2 studies in adult cancer patients (solid tumor or lymphoma [A5481001], mantle cell lymphoma [A5481002], and relapsed/refractory multiple myeloma [A5481004, in combination with bortezomib and dexamethasone]) have been completed with study reports available. One Phase 1/2 study in advanced breast cancer (A5481003, in combination with letrozole) has completed with a study report available. An additional Phase 1b dose-escalation study in Japanese patients with advanced cancer/ advanced breast cancer (A5481010, single agent, and in combination with letrozole) started enrollment in late 2012 and is ongoing. Two Phase 3 studies in advanced breast cancer patients, including A5481008 (in combination with letrozole) and A5481023 (in combination with fulvestrant and goserelin) have completed enrollment and are currently ongoing.

Pharmacokinetic (PK) parameters are available from all 74 patients enrolled in Protocol A5481001 following a single-dose (Day 1 of Cycle 1), and from 51 patients following multiple-dose administration (Day 8 of Cycle 1) of once daily doses ranging from 25 to 225 mg of palbociclib on Schedules 3/1 and 2/1. In addition, PK parameters are also available for 9 patients on Day 14 of Cycle 1 (from patients on Schedule 2/1) and 4 patients on Day 21 of Cycle 1 (from patients on Schedule 3/1). The exposure ($AUC_{(0\text{-}10hr)}$ and C_{max}) increased in a dose-proportional manner over the dose range of 25-225 mg QD following palbociclib administration on Days 1 and 8 of Cycle 1, although some variability (low to moderate) around these doses was observed particularly at the 150 mg QD dose level.[9]

PK data from Study A5481002 (mantle cell lymphoma population) indicated that palbociclib exposure at steady state in mantle cell lymphoma patients was similar to that observed in patients with solid tumor or lymphoma (Protocol A5481001).[10]

PK analysis of data from the Phase 1 portion of Study A5481003 (breast cancer, combination with letrozole) was conducted to evaluate the potential for drug-drug interaction (DDI) between palbociclib and letrozole. Letrozole is primarily metabolized by CYP2A6, and CYP3A represents a minor pathway of elimination. The results indicate a lack of DDI between palbociclib and letrozole when administered in combination. Results from the Phase 2 portion of the study demonstrated the addition of palbociclib to letrozole resulted in statistically significant, robust, and clinically meaningful improvement in progression-free survival (PFS) as compared with letrozole alone in the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer (20.2 months versus 10.2 months). Objective response and clinical benefit rates (42.9% vs. 33.3% and 81.0% vs. 58%, respectively) were also superior with the combination. The safety profile of the palbociclib plus letrozole combination was tolerable and manageable with uncomplicated Neutropenia

and Leukopenia as the most common adverse events and clinically insignificant effects on QTc interval when compared to letrozole alone. [11]

PK data from Studies A5481001, A5481003, and A5481010 indicate that palbociclib is slowly absorbed with a median time of maximum concentration (T_{max}) between 4 and 8 hours post-dose, and is slowly eliminated with an elimination half-life ($t_{1/2}$) ranging from 23.2 hours to 28.8 hours. Palbociclib accumulates after repeated daily dosing (median Rac ranged from 1.9 to 2.4), which was consistent with its terminal $t_{1/2}$. In Study A5481010, the median R_{ss} (the predicted accumulation to estimate linearity) was 1.1, indicating that palbociclib clearance does not change over time. In Study A5481003, palbociclib was shown to achieve steady-state concentrations following 8 days of QD dosing. The palbociclib geometric mean volume of distribution (V_z/F) was 2583 L in women with advanced breast cancer (Study A5481003), which is significantly greater than total body water (42 L), indicating that palbociclib extensively distributes to peripheral tissues.

As of December 2014, pharmacokinetic (PK) data have also been collected in 15 completed clinical pharmacology studies from healthy volunteers (A5481009, A5481011, A5481012, A5481015, A5481016, A5481017, A5481018, A5481020, A5481021, A5481022, A5481026, A5481032, A5481036, A5481038, and A5481040).

Results from palbociclib human mass balance study (A5481011) suggested the major route of [^{14}C]-palbociclib elimination was mainly via fecal excretion (74.1% of dose) with 17.5% of dose excreted in urine. The parent drug was the most abundant circulating entity following oral administration of [^{14}C]-palbociclib. The major circulating metabolite was a glucuronide conjugate of palbociclib (M22), and 3 major metabolites recovered in feces included a sulfamic acid of palbociclib (M11, PF-06754233), a carboxylic acid (M16) and a cyclopentyl ring-hydroxylated metabolite of the lactam (M17, PF-05089326). In vitro studies suggested that cytochrome P450 (CYP) 3A and sulfotransferase (SULT)2A1 were the major enzymes responsible for palbociclib metabolism. PF-05089326 was suggested to be approximately an equipotent inhibitor of CDK-4/6 relative to palbociclib in vitro and present at 18% and 10% of parent drug based on C_{max} and AUC_{inf}, respectively.[12] Since the systemic exposure of PF-05089326 was only approximately 10% of parent drug, and it also showed a lower unbound fraction than palbociclib, the PK of this metabolite was not characterized in subsequent clinical studies.

Palbociclib DDI study A5481012 suggested palbociclib is considered to be a weak time-dependent inhibitor of CYP3A based on the results that coadministration of palbociclib increased midazolam AUC_{inf} and C_{max} by 61% and 37% respectively.[13] Results from study A5481017 showed coadministration of strong CYP3A inducer rifampin decreased palbociclib AUC_{inf} and C_{max} by 85% and 70% respectively, relative to those when palbociclib was given alone.[14] Results from a DDI study of palbociclib with strong CYP3A inhibitor itraconazole (A5481016) suggested coadministration of itraconazole increased the palbociclib AUC_{inf} and C_{max} by approximately 87% and 34%, respectively.[15]

The effect of food on the exposure of palbociclib when administered as the commercial free base capsule was evaluated in healthy subjects (A5481021). Compared to palbociclib given under overnight fasted conditions, the AUC_{inf} and C_{max} of palbociclib increased by 21% and 38% when given with high-fat food, by 12% and 27% when given with low-fat food, and by 13% and 24% when moderate-fat food was given 1 hour before and 2 hours after palbociclib dosing. In addition, food intake significantly reduced the intersubject and intrasubject variability of palbociclib exposure. Based on these results, palbociclib commercial free base capsules should be taken with food.[16]

Results from palbociclib relative bioavailability study (A5481036) showed the final Phase 3/commercial free base capsules administered with moderate-fat food are bioequivalent to the isethionate capsules given under an overnight fasted condition and a minimal fasted condition, which represent the 2 extreme scenarios for compliant palbociclib dosing with regard to food intake in Study A5481003.[17] This finding supports the recommendation that palbociclib final Phase 3/commercial free base capsules should be administered with food in all ongoing and future studies.

The solubility of the palbociclib free base is pH dependent-palbociclib is water soluble at low pH (2.1-4.5), while the solubility dramatically decreases as pH rises above 4.5. Concomitant administration of agents which increase gastric pH can alter the solubility and absorption of palbociclib free base formulations.

A palbociclib DDI study (A5481038) was conducted to investigate the effect of a proton-pump inhibitor (PPI), a H_2-receptor antagonist (H_2RA) and a local antacid on bioavailability of palbociclib with the final Phase 3/commercial free base capsule forumulation under fed condition in healthy volunteers. The results demonstrated that a H_2RA famotidine given 10 hours before and 2 hours after palbociclib, or a local antacid Mi-Acid Maximum Strength Liquid given 2 hours before or 2 hours after palbociclib, had no impact on the exposure of palbociclib. Rabeprazole, a PPI given daily for 6 days before and 4 hours prior to palbociclib resulted in approximately 41% decrease in C_{max}, but had limited effect (13%) on AUC_{inf}.[18] In another healthy subject study, coadministration of a single dose of commercial free base capsule with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib AUC_{inf} and C_{max} by 62% and 80%, respectively, when compared to a single dose of palbociclib administered alone. Collectively, these antacid DDI data further support the requirement that the free base capsule of palbociclib should be taken with food.[19]

1.2.2. Safety

In Studies A5481001 and A5481002, the most commonly reported treatment related treatment-emergent adverse events (TEAEs) (≥20% of patients) of any grade, regardless of causality were fatigue (52.7% of patients); neutropenia (48.4%); nausea (35.2%); diarrhea and anemia (30.8% each); constipation (26.4%); decreased appetite (22.0%); and vomiting and thrombocytopenia (20.9% each). In Study A5481003, the most commonly reported TEAE of any grade, regardless of causality were neutropenia (73.7%); fatigue (46.3%); leukopenia (44.2%); anemia (34.7%); nausea (28.4%); diarrhea and arthralgia (24.2% for each); and hot flush (21.1%).[20] Neutropenia, leukopenia, and anemia were the most frequent treatment-related Grade 3/4 AEs in patients treated with the combination therapy of

palbociclib plus letrozole in Study A5481003. However, the reported AEs were reversible, non-cumulative, and clinically manageable. Given the known antiproliferative mechanism of action of palbociclib as a cell cycle inhibitor, myelosuppression is the on-target hematologic toxicity.

The preliminary results from an ongoing Phase 1 study in Japanese patients (A5481010) showed that the safety profile with single-agent palbociclib in Japanese was similar to that in non-Japanese patients; additionally, no new safety signals were identified in Japanese patients who received palbociclib in combination with letrozole.

A quantitative analysis of the relationship between the QTc interval and the plasma concentrations of palbociclib in patients with advanced cancer was conducted using data from Studies A5481001, A5481002, and A5481003 following steady state doses ranging from 25-225mg. At the mean or median steady state C_{max} of palbociclib following a therapeutic dosing schedule (125 mg QD on schedule of 3 weeks on treatment/1 week off treatment), the mean study-corrected QTc (QTcS) increase was 5.6 msec, with the upper bound of the one-sided 95% CI falling below 10 msec, suggesting that QT interval prolongation is not a safety concern with palbociclib treatment with the recommended dosing regimen. In addition, palbociclib had no effect on heart rate.[21]

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

1.2.3. Study Rationale

This Phase 1 China-only PK study (A5481019) is intended to support the CFDA regulatory filing requirement of palbociclib, and is designed to evaluate the PK profile and safety of palbociclib as combination therapy with letrozole in Chinese patients with ER(+), HER2(-) ABC. In addition, efficacy will be evaluated as one of the secondary objectives.

1.2.3.1. Rationale for Palbociclib Administration Schedule

Palbociclib has been administered and examined 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).

Overall, the adverse events (AEs) reported in this study were manageable and reversible. The dose-limiting toxicities (DLTs) that occurred during this study were similar between the two dosing schedules and consisted of myelotoxic events, ie, neutropenia, thrombocytopenia, and/or anemia. The myelosuppression was not irreversible, cumulative, or complicated, and it resulted in permanent treatment discontinuation in only 1 patient.

For patients who received palbociclib QD administered on Schedule 3/1, 37 patients were evaluable for response, 13 patients (35%) had an overall best response of stable disease for at least 2 cycles. Stable disease lasted ≥4 cycles in 10 patients (27%) and ≥10 cycles in 6 patients (16.2%).

For the patients who received palbociclib QD administered on Schedule 2/1, 31 of the 33 patients were evaluable for response. One patient with testicular cancer had a partial response (PR) to palbociclib 200 mg QD. Six patients (19%) maintained stable disease for ≥4 cycles, and 3 patients (10%) maintained stable disease for ≥10 cycles.

While the safety profiles of the two schedules were comparable, greater long-term antitumor activity was observed with Schedule 3/1; therefore this regimen was selected for further clinical development. The RP2D for Schedule 3/1 was determined to be 125 mg QD.

Study A5481002 was conducted to evaluate the pharmacodynamics, clinical activity and safety of palbociclib administered at 125 mg QD using Schedule 3/1 in patients with previously treated mantle cell lymphoma (MCL). Seventeen patients have been enrolled in this study in which 1 complete response and 2 partial responses were observed. PET-CT was used in this study along with relevant tumor tissue biomarkers to confirm the proof of mechanism of action of palbociclib as MCL is a disease characterized by overexpression of Cycline D1. The safety profile was similar to that observed in the dose escalation study.

Based on the above data, Schedule 3/1 was selected for Study A5481019.

1.2.3.2. Rationale for Palbociclib Dose

Palbociclib was evaluated in a series of in vitro and in vivo genetic toxicity studies. Palbociclib was not mutagenic in bacteria or clastogenic in the structural chromosome aberration assay. Kinetochore staining in an in vitro micronucleus assay determined that positive micronucleus results in vitro and in vivo were due to aneugenicity. It is well accepted that aneugens induce their effect by a threshold mechanism[22,23,24] for which a NOEL can be defined. A NOEL for micronucleus induction was identified from an in vivo bone marrow rat micronucleus assay with palbociclib. Significant increases in micronucleated polychromatic erythrocytes were identified at doses ≥100 mg/kg/day in the male only; a NOEL for micronuclei formation was identified at 50 mg/kg/day in males and 400 mg/kg/day in females given palbociclib for 3 weeks, with associated systemic Day 21 unbound AUC values of 2163 and 1388 ng•hr/mL, respectively, offering up to an 8-fold margin over unbound systemic AUC exposure related to the human clinical dose of 125 mg QD (274 ng•hr/mL) which will be administered in this study. Based on the lack of direct DNA interaction and the expected safety margin for aneugenic activity, there are no perceived genetic toxicity risks to humans at doses up to 125 mg QD, allowing for multiple dosing in healthy volunteers and cancer patients.

Based on Phase 1 Study A5481001 in cancer patients, 125 mg QD of palbociclib was determined to be the maximally tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) on the 3/1 schedule. In Study A5481001, a total of 22 advanced cancer patients were enrolled on the 3/1 schedule to the 125 mg QD cohorts. As of 9/1/2013, palbociclib has been administered chronically to over 270 advanced cancer patients in Pfizer-sponsored trials at doses ranging from 25 – 225 mg/day, including 74 patients in Study A5481001, 17 patients in Study A5481002, 95 patients in Study A5481003, 51 patients in Study A5481004, 42 patients in Study A5481008 (includes both patients treated with palbociclib and placebo in this double-blind, placebo-controlled study), and 17 patients in Study A5481010. Over

150 of those patients received daily doses of at least 125 mg/day. In addition, 125 mg was the dose used in pivotal Phase 2 Study A5481003 for ER(+) HER2(-) advanced breast cancer.

Based on the safety data of palbociclib and prior clinical experience as described above, a dose of 125 mg/day of palbociclib as a single dose or once daily at the 3/1 schedule is selected to be administered in combination with letrozole in Chinese patients with advanced breast cancer in this study. A minimum of approximately 25 patients will be enrolled to the study. Patients may be replaced if there are less than 12 patients completing the single-dose and multiple-dose PK sample collections without dosing interruption or dose modification. For single-dose PK asessement, on Day 1 of Lead-in phase, patients will receive oral single dose of 125 mg palbociclib in combination with 2.5 mg letrozole; letrozole dosing QD will continue from Day 2 - Day 5. From Day 1 of Cycle 1 and thereafter, patients will receive palbociclib 125 mg orally once daily for 3 weeks followed by 1 week off treatment in combination with 2.5 mg letrozole orally once daily continuously in 28-day cycles.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

- To determine single-dose and multiple-dose PK profiles of palbociclib in combination with letrozole in Chinese patients with ER(+)/HER2(-) advanced breast cancer who have not received any prior systemic anti-cancer therapy for their advanced disease.

Secondary Objectives

- To evaluate safety of palbociclib in combination with letrozole in this patient population.
- To evaluate efficacy of palbociclib in combination with letrozole in this patient population.
- To evaluate trough plasma concentration of letrozole after multiple dosing.
- To evaluate biomarker changes post palbociclib treatment and their correlation with drug exposure and efficacy endpoints if data permit.

2.2. Endpoints

Primary Endpoint

- Single-dose (SD) PK parameters: C_{max}, AUC_{10}, AUC_{24} (=$AUC_{sd,\tau}$), AUC_{last}, AUC_{inf}, T_{max}, V_z/F, K_{el}, $t_{1/2}$, MRT, CL/F.
- Multiple-dose (MD) PK parameters: $C_{ss,min}$, $C_{ss,max}$, $C_{ss,av}$, $AUC_{ss,\tau}$, $T_{ss,max}$, V_z/F, $t_{1/2}$, CL/F, PTF (=DF), R_{ac}, and R_{ss}.

Secondary Endpoints

- Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.0) , timing, seriousness and relationship to study therapy;
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.0) and timing;
- Corrected QT interval (QTc);
- Progression-Free Survival (PFS);
- Objective Response (OR: Complete Response [CR] or Partial Response [PR]);
- Disease Control (DC: CR + PR + Stable disease ≥24 weeks);
- Duration of Response (DR);
- 1-year PFS Probability;
- Trough plasma concentration of letrozole;
- Skin biomarkers phosphorylated retinoblastoma protein (pRb) and Ki67 expression; blood biomarker thymidine kinase [TK] activity.

3. STUDY DESIGN

This is a single-country, non-randomized, open-label, single-arm, multicenter Phase 1 clinical trial which will evaluate PK, safety and efficacy of palbociclib in combination with letrozole in postmenopausal Chinese women with ER(+)/HER2 (-) ABC.

A minimum of approximately 25 patients will be enrolled to the study and patients may be replaced if there are less than 12 patients completing the single-dose and multiple-dose PK sample collections without dosing interruption or dose modification.

Single-dose PK (Lead-in phase, total 5 days) will be conducted prior to multiple-dose PK (Cycle 1). On Day 1 of the single-dose PK part (Lead-in phase), patients will receive a single oral dose of palbociclib 125 mg and letrozole 2.5 mg. From Day 2 to Day 5, patients will receive letrozole 2.5 mg alone once daily as a background therapy. From Cycle 1 Day 1 (C1D1), patients will receive palbociclib 125 mg once daily orally for 3 weeks followed by 1 week off treatment and letrozole 2.5 mg once daily orally continuously. Patients will remain on study treatment with combination treatment of palbociclib and letrozole until disease progression, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. However, patients may continue the study treatment beyond the time of RECIST-defined disease progression at the discretion of the investigator if that is considered to be in the best interest of the patient and as long as no new anticancer treatment is initiated. In this case, the patient would continue with routine safety relevant assessments as per the Schedule of Activities for the active treatment period.

Patients will be screened within 28 days of the first dose of study medication. Patients will be admitted to the clinical research unit (CRU) at least 12 hours prior to Day 1 dosing in Lead-in phase and remain in the CRU until at least 72 hours post-dose on Day 4 in Lead-in phase for PK samplings before discharge (the duration of confinement is subject to change given the availability of CRU). Patients will return to the CRU as outpatient visits on Day 5 (Lead-in phase) for morning PK sample collection at 96 hours post-dose and on C1D1 for predose morning PK sample collection (120 hours post single dose). During Cycle 1, patients will visit the CRU for hematology evaluation on Day 14 and trough PK sample collection (predose) on Day 19. Patients will return to the CRU on C1D20 for trough PK sample collection (predose) and remain in the CRU until C1D24 for PK sample collection before discharge (the duration of confinement is subject to change given the availability of CRU). Patients will visit the CRU on Days 25, 26 of Cycle 1and C2D1 for morning trough PK sample collection (predose).

Blood samples for determination of palbociclib concentrations will be collected at 2, 4, 6, 8, 10, 24, 48, 72, 96, and 120 hours after single-dose palbociclib administration for single-dose PK in Lead-in phase and after palbociclib dose on C1D21 for multiple-dose PK. Trough blood samples (predose) for both palbociclib and letrozole will be collected on Days 19-21 of Cycle 1. An additional trough blood sample (predose) for letrozole will be collected on C2D1.

Disease assessments will be performed every 12 weeks (±7 days) from C1D1. Patients with bone lesions identified at baseline will also have repeat bone scans performed every 24 weeks (±7 days) from C1D1. Each assessment will be performed as scheduled according to the calendar regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. Tumor assessments will be performed until radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. A series of incomplete disease assessments will result in censoring of PFS back to the time of the last full assessment that did not show disease progression.

The study also includes translational components aimed at characterizing alterations in proteins relevant to the cell cycle, drug targets, and patient response over time. Longitudinal monitoring of palbociclib pharmacodynamic marker modulation, such as phosphorylated retinoblastoma protein (pRb) and Ki67 expression using skin biopsies and thymidine kinase (TK) activity using serum samples will allow characterizing the relationship among PK, biomarker, and patient clinical response. The duration and magnitude of cell cycle inhibition after palbociclib treatment may also be obtained. This biomarker analysis will be critical for better understanding of the mechanism of action of palbociclib in breast cancer patients, and may also potentially identify patients with better response to palbociclib treatment.

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 protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriately qualified 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. Postmenopausal adult (ages 18-65 years, inclusive) Chinese women with proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease not amenable to resection or radiation therapy with curative intent and for whom chemotherapy is not clinically indicated. The details of criteria are specified below:

    a. Postmenopausal women defined as women who have undergone:

        i. Prior documented bilateral surgical oophorectomy; or

        ii. Spontaneous cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause, confirmed with follicle-stimulating hormone (FSH) and estradiol blood levels in their respective postmenopausal ranges.

    b. Documentation of histologically or cytologically confirmed diagnosis of ER(+) breast cancer based on local laboratory results.

    c. Documentation of HER2(-) breast cancer based on local laboratory results.

    d. Previously untreated with any systemic anti-cancer therapy for their locoregionally recurrent or metastatic ER+ disease.

2. Measurable disease as defined per RECIST v.1.1 or bone-only disease (with bone lesions confirmed by computed tomography [CT], Magnetic Resonance Imaging [MRI] or bone X-ray). Tumor lesions previously irradiated or subjected to other locoregional therapy will only be deemed measurable if disease progression at the treated site after completion of therapy is clearly documented.

3. Eastern Cooperative Oncology Group performance status 0-1.

4. Adequate organ and marrow function defined as follows:

    - ANC ≥1,500/mm3 (1.5×10^9 /L);

    - Platelets ≥100,000/mm3 (100×10^9 /L);

- Hemoglobin ≥9 g/dL (90 g/L);
- Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≥ 60 mL/min as calculated using the method standard for the institution;
- Total serum bilirubin ≤1.5 x ULN (≤3.0 x ULN if Gilbert's disease);
- AST and/or ALT ≤3 x ULN (≤5.0 x ULN if liver metastases present);
- Alkaline phosphatase ≤2.5 x ULN (≤5.0 x ULN if bone or liver metastases present).

5. Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to baseline severity or NCI CTCAE version 4.0 Grade ≤1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion)
6. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.
7. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all the pertinent aspects of the trial prior to enrollment.

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. HER2-positive tumor as defined by documentation of erbB-2 gene amplification by FISH (as defined by a HER2/CEP17 ratio ≥2) or chromogenic in situ hybridization (CISH, as defined by the manufacturer's kit instruction) or documentation of HER2-overexpression by IHC (defined as IHC3+, or IHC2+ with FISH or CISH confirmation) based on local laboratory results.
2. Patients with advanced, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement).
3. Known active uncontrolled or symptomatic CNS metastases, as indicated by clinical symptoms, cerebral edema, spinal cord compression, carcinomatous meningitis, leptomeningeal disease and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated and are clinically stable off anticonvulsants and steroids for at least 4 weeks before the first dose of palbociclib.
4. Prior neoadjuvant or adjuvant treatment with a non-steroidal aromatase inhibitor (ie, anastrozole or letrozole) with disease progression or recurrence while on or within 12 months from completing treatment.
5. Prior treatment with any CDK4/6 inhibitor.

6. Known malabsorption syndrome or other condition that may impair absorption of palbociclib.

7. Patients treated within the last 7 days prior to study entry with:

   - Food or drugs that are known to be strong CYP3A4 inhibitors (ie, amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit or grapefruit juice).

   - Drugs that are known to be strong CYP3A4 inducers (ie, carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort).

   - Drugs that are known to prolong the QT interval.

8. Major surgery, chemotherapy, radiotherapy, any investigational agents, or other anti-cancer therapy within 2 weeks before study entry. Patients who received prior radiotherapy to ≥25% of bone marrow are not eligible independent of when it was received (see Appendix 5).

9. Diagnosis of any other malignancy within 3 years prior to study entry, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.

10. QTc interval >480 msec (based on the mean value of the triplicate screening electrocardiogram [ECGs]); family or personal history of long or short QT syndrome; history of clinically significant ventricular dysrhythmias, or currently under treatment with anti-arrhythmic medication or implanted defibrillation device for ventricular dysrhythmias.

11. Uncontrolled electrolyte disorders that can compound the effects of a QTc-prolonging drug (eg, hypocalcemia, hypokalemia, hypomagnesemia).

12. Any of the following within 6 months of study entry: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE version 4.0 Grade ≥2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.

13. Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection.

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

15. Active and clinically significant bacterial, fungal or viral infection including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

16. Other severe acute or chronic medical or psychiatric condition or 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.

17. 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 trial.

18. Participation in any other studies within 4 weeks before study entry and/or during participation in the active treatment phase of the trial.

19. Recent or active suicidal ideation or behavior.

4.3. Randomization Criteria

- Patients will be randomized on Day -1 into two groups associated with different skin biopsy schedules, provided they have satisfied all patient selection criteria.

- The investigators or their pre-specified designee will randomize eligible patients by interactive randomization technology (IRT) as described in the Study Reference Manual.

- The central computerized system will provide the randomization number and assignment of skin biopsy schedule.

4.4. Life Style Guidelines

The following guidelines are provided:

4.4.1. Alcohol, Caffeine, Chinese Herbal Medicine and Exercise for PK Evaluation

- Patients will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the last pharmacokinetic sample. An alcohol breath test is not required but may be conducted at the discretion of the investigator.

- Patients will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the last pharmacokinetic sample .

- Patients will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

- No Chinese herbal medicines will be allowed during PK portion.

4.4.2. Meals and Dietary Restrictions for PK Evaluation

- Palbociclib and letrozole should be administered together with food.

- On Day 1 in Lead-in phase and Day 21 in Cycle 1 when intensive PK samples are collected, similar breakfast should be provided to patients approximately 30 minutes prior to the administration of palbociclib (breakfast started at approximately 0930 AM). Breakfast will be consumed within a 20-minute period with study drugs administered approximately 10 minutes after completion of the meal. At least 80% of the provided breakfast should be consumed prior to palbociclib administration. The provided breakfast should be moderate-fat standard-calorie meal (approximately 15% protein, 50% carbohydrate, 35% fat diet for a total of 500-700 calories). Lunch and dinner will be provided approximately 4 hours and 9 hours after palbociclib dosing.

- Non-caffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices – see below) may be consumed with meals and the evening snack.

- An evening snack may be permitted.

- Patients will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the first dose of study medication until collection of the last PK blood sample.

- While confined, the recommended total daily nutritional composition should be approximately 50% carbohydrate, 35% fat and 15% protein. The daily caloric intake per patient should not exceed approximately 3200 kcal.

4.5. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list in the team sharepoint study portal space. 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 number, contact information for the investigational site and contact details for a help desk 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 patients participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used 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 study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the patient directly and if a patient calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular patient or affect the order in which patients are enrolled. The investigator will assign patient numbers sequentially to the patients as they are screened for the study.

The study will have 1 treatment group. On Day 1 in the Lead-in phase (single-dose PK part), patients will receive a single oral dose of palbociclib 125 mg and letrozole 2.5 mg. From Day 2 to Day 5, patients will receive letrozole 2.5 mg alone once daily as a background therapy. On Cycle 1 Day 1 (C1D1), patients will start the first cycle of combination treatment, palbociclib 125 mg once daily orally for 3 weeks followed by 1 week off treatment and letrozole 2.5 mg once daily orally continuously. Patients will remain on study treatment with combination treatment of palbociclib and letrozole until disease progression, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first.

5.2. Drug Supplies

The investigational drug used in the course of this trial is palbociclib. In addition, all patients will receive letrozole. Both of the medications will be supplied by the sponsor. Study Centers will receive a supply of the appropriate investigational product after site activation. Re-supplies will be made during the course of the study. The study monitor should be contacted for any issues related to investigational product supplies.

5.2.1. Formulation and Packaging

5.2.1.1. Palbociclib

Palbociclib will be supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base. The sponsor will supply the oral drug formulation to sites in HDPE bottles containing 75 mg, 100 mg, or 125 mg capsules. The capsules can be differentiated by their size and color (see below).

Table 4. Palbociclib Capsule Characteristics

Dosage	Capsule color	Capsule size
75 mg	Sunset Yellow/Sunset Yellow	2
100 mg	Caramel/Sunset Yellow	1
125 mg	Caramel/Caramel	0

5.2.1.2. Letrozole

Commercially available letrozole 2.5 mg film-coated tablets will be sourced locally. Complete information about letrozole formulation can be found in the local package insert.

5.2.2. Preparation and Dispensing

5.2.2.1. Palbociclib

Palbociclib will be provided in non-patient specific bottles containing either 75 mg, 100 mg or 125 mg capsules. The patient number should be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient. 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 study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit. Returned unused medication MUST NOT be re-dispensed to the patient. Detail information is provided in the study manual.

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.

Only one capsule strength will be dispensed to the patient at each dispensing visit. In the event of dose modification, request should be made of the patient to return all previously dispensed medication to the clinic, and new capsules will be dispensed.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

5.2.2.2. Letrozole

Letrozole should be prepared and dispensed according to the package insert or standard practice at the study site. The patient number should be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient. 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 study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

5.2.3. Administration

5.2.3.1. Palbociclib

Palbociclib will be orally administered daily for 3 weeks followed by 1 week off treatment (Schedule 3/1), defining a treatment Cycle that is 28 days in duration.

Palbociclib will be orally administered once daily in the morning with food. On the intensive PK days (Day 1 in Lead-in phase and Day 21 in Cycle 1), similar breakfast with moderate fat and standard calories should be provided to patients approximately 30 minutes prior to

administration of palbociclib (breakfast started at approximately 0930 AM). Breakfast will be consumed within a 20-minute period with study drugs administered approximately 10 minutes after completion of the meal. At least 80% of the provided breakfast should be consumed prior to palbociclib administration. The provided breakfast should be moderate-fat standard-calorie meal (approximately 15% protein, 50% carbohydrate, 35% fat diet for a total of 500-700 calories). Lunch and dinner will be provided approximately 4 hours and 9 hours after palbociclib dosing. If intensive PK assessments are conducted in a later cycle for any reason, the same requirement for breakfast intake is applied. Safety evaluation (vital signs, laboratory safety and ECG) should be conducted before food intake.

Patients should be instructed to swallow palbociclib capsules whole and not to chew 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 should be instructed to record daily administration of the study drugs in a patient diary.

Patients experiencing investigational product related toxicity may have their dose modified according to Section 5.2.4.2.

5.2.3.2. Letrozole

Letrozole will be administered orally once daily continuously together with palbociclib. From Day 2 to 5 in Lead-in phase, during the off-treatment week of palbociclib, and in the event of palbociclib dosing interruption, letrozole alone will be administered.

5.2.3.3. General rules

For both palbociclib and letrozole:

- Patients who miss a day's dose entirely must be instructed NOT to "make it up" the next day.
- Patients who vomit anytime 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 Section 5.2.5 for further details on medication errors and overdose.

5.2.4. Recommended Dose Modification

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of study drugs (palbociclib or letrozole) may need to be adjusted as described in the following sections. Depending on the nature of the toxicity observed, dosing adjustment may be required for just one or both study drugs in the combination. In the event treatment interruption is deemed necessary for just one of the study drugs in the combination, treatment with the other study drug will continue as planned.

5.2.4.1. Letrozole

No dose adjustment for letrozole is permitted but dosing interruptions are allowed. Treatment interruption for letrozole-related toxicities will be performed as per the investigator's best medical judgment.

Patients discontinuing letrozole treatment due to treatment-related toxicity will be discontinued from the study.

5.2.4.2. Palbociclib

In the event of significant treatment-related toxicity, palbociclib dosing may be interrupted or delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

Dose modifications may occur in three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

5.2.4.2.1. Dosing Interruptions

Patients experiencing the following adverse events should have their treatment interrupted/delayed:

- Uncomplicated Grade 3 neutropenia (ANC<1000/mm^3);
- Grade 3 neutropenia (ANC<1000/mm^3) associated with a documented infection or fever ≥38.5°C;
- Grade 4 neutropenia (ANC<500/mm^3);
- Grade 4 thrombocytopenia (Platelet count <25,000/mm^3);
- Grade ≥3 non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment);
- Grade 3 QTc prolongation (QTc ≥501 msec on at least two separate ECGs).

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the Investigator. Criteria required before treatment can resume are described in Section 5.2.4.2.2.

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not to be replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Section 5.2.4.2.3 unless expressly agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction is applied in the same cycle, the patient will need to return to the clinic to receive new drug supply.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, non-cancer related surgery) lasting >2 weeks, treatment resumption will be decided in consultation with the sponsor.

5.2.4.2.2. Dose Delay

Retreatment following treatment interruption for treatment related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- Platelet count ≥50,000/mm^3;
- ANC ≥1000/mm^3 and no fever;
- Grade ≥3 treatment-related non-hematologic AEs (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment), with the exception of alopecia, 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 <501 msec and potential reversible causes (eg, electrolyte imbalance, concomitant medications known to prolong QTc) corrected. If QTc remains above 480 msec, electrocardiogram (ECG) should be monitored more frequently as per the investigator's best medical judgement until QTc ≤480 msec.

If a treatment delay results from decline in hematologic parameters, the frequency of blood count assessments should be increased as clinically indicated.

If these parameters are met within 2 weeks of treatment interruption or cycle delay, palbociclib may be resumed. Refer to Section 5.2.4.2.3 Dose Reductions for adverse events requiring dose reduction at the time of treatment resumption.

If these parameters have not been met after 2 weeks of dosing interruption (including the scheduled 1 week off treatment) or 2 weeks of cycle delay, permanent discontinuation of palbociclib treatment should be considered. Treatment resumption for patients recovering from treatment-related toxicity after >2 weeks of treatment interruption or cycle delay who are deriving clinical benefit per the investigator's best medical judgment is left at the investigator's discretion.

In the event that the start of a new cycle is delayed due to treatment-related toxicity, procedures required on Day 1 of the given cycle will be performed when palbociclib is resumed. New cycle Day 1 procedures (ie, physical examination, ECOG performance status, ECG, Qualify of Life questionnaires, blood chemistry, hematology) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated (1) if not required to determine whether study drug may be resumed and (2) if performed within 7 days prior to study drug resumption.

5.2.4.2.3. Dose Reductions

Following dosing interruption or cycle delay the palbociclib dose may need to be reduced when treatment is resumed.

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.

Dose reduction of palbociclib by 1 and, if needed, 2 dose levels (Table 5) will be allowed depending on the type and severity of toxicity encountered. Patients requiring more than 2 dose reductions will be discontinued from the study.

All dose modifications/adjustments must be clearly documented in the patient's source notes and case report form pages (CRF) for Investigational product administration.

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

Table 5. Available Dose Levels

Dose Level	Palbociclib for 3 out of 4 weeks (3/1 schedule)	Letrozole on a continuous daily dosing schedule
Starting Dose	125 mg/d	2.5 mg/d
-1	100 mg/d	2.5 mg/d
-2	75 mg/d*	2.5 mg/d
Discontinue Study Treatment		

* Palbociclib dose reduction below 75 mg/d is not allowed.

Palbociclib recommended dose modifications for treatment related toxicities requiring treatment interruption/delay or persisting despite optimal medical treatment are described in Table 6 and Table 7.

Table 6. Palbociclib Dose Modifications for Treatment Related Toxicities Requiring Treatment Interruption/Delay or Persisting Despite Optimal Medical Treatment.

Type and Grade of Toxicity	Restart Palbociclib Treatment at:
Uncomplicated Grade 3 neutropenia *(500/mm^3≤ANC<1000/mm^3)*	Same dose level
Grade 3 neutropenia *(500/mm^3≤ANC<1000/mm^3)* **associated with a documented infection or fever ≥38.5°C**	↓ 1 Dose Level
Grade 4 neutropenia *(ANC<500/mm^3)*	↓ 1 Dose Level
Grade 4 thrombocytopenia *(Platelet count <25,000/mm^3)*	↓ 1 Dose Level
Grade ≥3 non-hematologic toxicity *(including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment)*	↓ 1 Dose Level

Table 7 Palbociclib Dose Modifications for Hematologic Toxicities (by CTCAE Grade and on Day of Treatment)[a]

Day of treatment	CTCAE Grade	Dose modifications
Cycle 1 Day 14	Grade 1, 2, and 3	No dose adjustment is required
	Grade 4[b] Grade 3[c] with documented infection or fever ≥38.5°C	Withhold until recovery to Grade ≤2, then resume at next lower dose at start of next cycle
Cycle 1 Day 21	Grade 1, 2, and 3	No dose adjustment is required
	Grade 4[b] Grade 3[c] with documented infection or fever ≥38.5°C	Withhold until recovery to Grade ≤2, then resume at next lower dose at start of next cycle
Cycle 2 Day 1	Grade 1 and 2	No dose adjustment is required
	Grade 3[b]	Withhold until recovery to Grade ≤2, then resume at current dose
	Grade 4[b] Grade 3[c] with documented infection or fever ≥38.5°C	Withhold until recovery to Grade ≤2, then resume at next lower dose
Cycle 2 Day 21	Grade 1, 2, and 3	No dose adjustment is required

	Grade 4[b] Grade 3[c] with documented infection or fever ≥38.5°C	Withhold until recovery to Grade ≤2, then resume at next lower dose at start of next cycle
Day 1 of subsequent cycles	Grade 1 and 2	No dose adjustment is required
	Grade 3[b]	Withhold until recovery to Grade ≤2, then resume at current dose
	Grade 4[b] Grade 3[c] with documented infection or fever ≥38.5°C	Withhold until recovery to Grade ≤2, then resume at next lower dose

Grading according to CTCAE Version 4.0.
ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events.

a. Monitor complete blood count prior to starting Palbociclib and on Day 14 and 21 of the first cycle. Obtain complete blood count at the start of, and on Day 21 of the second cycle. Continue monthly monitoring of complete blood count at the beginning of each cycle for at least 4 subsequent cycles. Once complete blood count has stabilized, monitor as clinically indicated.
b. Except lymphopenia (unless associated with clinical events, eg, opportunistic infections).
c. Patients experiencing uncomplicated Grade 3 neutropenia (ANC<1000/mm^3) should still have their treatment interrupted/delayed until recovery to Grade ≤2, then resume at the same current dose. Patients with Grade 3 neutropenia (ANC<1000/mm^3) associated with a documented infection or fever ≥38.5°C should have their treatment interrupted/delayed until recovery to Grade ≤2 and fever is no longer present, then resume at next lower dose.

QTc prolongation management

In the event of QTc prolongation, possible alternative reversible causes such as serum electrolytes abnormalities, or usage of concomitant medications with the potential to prolong the QT interval should be evaluated.

If such reversible causes are identified, then they should be corrected accordingly (ie, correction of electrolyte abnormalities with supplements to within normal limits and/or discontinuation (if possible) of concomitant medications known to prolong the QT interval).

Recommended dose modifications in the event of QTc prolongation are provided in Table 8.

Table 8. Palbociclib Dose Modifications in the Event of QTc Prolongation

	Toxicity (NCI CTCAE Grade, Version 4.0)		
	Grade 2 QTc prolongation	**Grade 3 QTc prolongation**	**Grade 4 QTc prolongation**
Reversible cause identified	Treat reversible cause Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc ≤480 msec Continue at the same dose level (1)	Treat reversible cause Withhold treatment until QTc<501 msec Resume treatment at the same dose level. Monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec.	Permanently discontinue
No reversible cause identified	Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc≤480 msec Continue at the same dose level (1)	Withhold treatment until QTc<501 msec Resume treatment at the next lower dose level (2) Monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec.	Permanently discontinue

1. If the QTc remains above 480 msec more than 2 cycles or if Grade 2 QTc prolongation recurs in the absence of other alternative causes or despite correction of alternative causes, dose adjustment and/or discontinuation should be considered in consultation with a cardiologist and the sponsor's medical monitor, taking into account the emerging safety data from palbociclib trials and the investigator's best medical judgment.

2. If the Grade 3 QTc prolongation occurs again after one dose reduction, further dose adjustment and/or discontinuation should be discussed with sponsor's medical monitor in consultation with a cardiologist, taking into consideration the emerging safety data from palbociclib trials and the investigator's best medical judgment.

5.2.5. Medication Errors and Overdose

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 adverse event (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 a medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the adverse event (AE) page and, if applicable, any associated AEs are captured on an AE CRF page.

5.2.6. Compliance

Patients will be required to return all bottles of palbociclib and tablets of letrozole as well as the completed patient dosing diary at the beginning of each cycle for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle. The number of remaining capsules and tablets will be documented and recorded.

To be considered compliant, each study patient must have received at least 80% of the planned number of doses of primary therapy based on the number of days of actual dose administration. Dose adjustments must follow instructions provided in the dose adjustment guidelines section.

5.3. Drug Storage and Drug Accountability

Storage conditions stated in the Study Reference Safety Document (ie, Investigator's Brochure (IB), or Local Product Document (LPD)) will be superseded by the label storage.

Investigators and site staff are reminded to check temperatures daily (ie, manually or by using alarm system to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for both the room storage and refrigerator storage. Any excursions should be reported to the sponsor and addressed according to appropriate standard operating procedures.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product (palbociclib or letrozole) MUST be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

At the end of the trial, the sponsor will provide instructions as to disposition of any unused investigational product. If the sponsor authorizes destruction at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the sponsor. Destruction must be adequately documented.

5.3.1. Palbociclib

Palbociclib capsules should be stored at controlled room temperature (15-30°C) in their original container.

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication should be stored separately from medication that needs to be dispensed.

To ensure adequate records, palbociclib capsules will be accounted for as instructed by the sponsor. Patients are requested to return previously dispensed containers as well as their

completed patient dosing diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit.

5.3.2. Letrozole

Letrozole tablets must be stored according to the instructions detailed in the local package insert.

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication should be stored separately from medication that needs to be dispensed.

To ensure adequate records, letrozole tablets will be accounted for as instructed by the sponsor. Patients are requested to return previously dispensed containers as well as their completed patient diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit.

5.4. Concomitant Medications

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. Any medications including Chinese or other herbal medicines or supplements, vitamins, or treatment taken by the patient from 28 days prior to the start of study treatment and up to 28 days following the last dose of investigational product and the reason for their administration must be recorded on the CRF.

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral), does not need to be recorded. Anesthetics used for any surgical procedures performed during the patient's participation in the study can be recorded as "unspecified anesthesia" on the concomitant treatment records; it is not necessary to list the specific anesthetics. Palliative and supportive care for cancer-related symptoms will be offered to all patients in this study.

5.4.1. Prohibited Medications

The following treatments are prohibited throughout the duration of the active treatment phase:

- **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 active treatment phase. In general, any drugs containing "for the treatment of breast cancer" on the product insert are not permitted on 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. Co-administration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of palbociclib in humans. Data from a drug-drug interaction (DDI) study in healthy subjects indicated that coadministration of multiple 200-mg doses of the strong CYP3A inhibitor itraconazole with a single 125-mg palbociclib dose increased

palbociclib total exposure (AUC_{inf}) and the peak exposure (C_{max}) by approximately 87% and 34%, respectively, relative to a single 125-mg palbociclib dose given alone. Data from a DDI study in healthy subjects indicated that coadministration of multiple 600-mg doses of the strong CYP3A inducer rifampin with a single 125-mg palbociclib dose decreased palbociclib AUC_{inf} and C_{max} by 85% and 70%, respectively, relative to a single 125-mg palbociclib dose given alone. Use of food or drug that are CYP3A4 inhibitor or inducers are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first PK sample until the completion of all required PK samplings. After the completion of all required PK sample collections, the concurrent use of strong (includes some moderate) CYP3A4 inhibitors/inducers listed below is still not allowed in the study:

- Strong CYP3A inhibitors, including but not limited to 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 but not limited to carbamazepine, phenytoin, primidone, rifampin, rifapentin, and St. John's wort.

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

- **Drugs known to prolong the QT interval** are prohibited during the active treatment phase. Refers to Appendix 6 for a list of drugs known to predispose to Torsade de Pointes.

- **Hormone replacement therapy**, topical estrogens (including any intra-vaginal preparations), **megestrol acetate** and **selective estrogen-receptor modulators** (eg, raloxifene) are prohibited during the active treatment phase.

- **Proton-pump inhibitor (PPI):** the concomitant use of PPIs (including but not limited to, dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) with palbociclib is prohibited from at least 10 days before the first PK sample until the completion of all required PK samplings. If an acid-lowering agent is needed during this period, H_2-receptor antagonists and local antacids are allowed with staggered dosing regimens. Detailed recommendations about the use of acid-reducing agents are provided under Section 5.4.3.

- No Chinese or other herbal medicines will be allowed during PK portion. No Chinese anti-cancer herbal medicines will be allowed after the PK portion (Cycle 1).

5.4.2. Medications Not Recommended

The following treatments are not recommended throughout the duration of the active treatment phase. Alternative therapies should be considered whenever possible. If usage of the following treatments is deemed necessary, consultation and agreement with the sponsor's medical monitor is required prior to treatment initiation.

- **Moderate CYP3A Inducers:** The concurrent use of moderate CYP3A inducers such as dexamethasone or modafinil is not recommended.

- **Chronic immunosuppressive therapies** should be avoided, including systemic corticosteroids. Steroids given for physiological 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 use of **Chinese or other herbal medicine** is not recommended during the active treatment phase and is prohibited during PK portion of the study. Any usage of Chinese or other herbal medicines should be recorded.

5.4.3. Permitted Medications

The following treatments are permitted throughout the duration of the active treatment phase:

- **Standard therapies** for pre-existing medical conditions, medical and/or surgical complications, and palliation. Any medication intended solely for supportive care (eg, analgesics, antidiarrheals, antidepressants) may also be used at the investigator's discretion. All medications should be recorded.

- **Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors** for the treatment of osteoporosis or management of existing bone metastases may be continued for patients who have been receiving them at a stable dose for at least 2 weeks prior to study entry. However the need to initiate or increase the dose of these therapies during the study will be considered as indicative of disease progression leading to the discontinuation of patient unless disease progression can be completely ruled out and the exact reason for the use of these therapies clearly documented in the patient's source documentation.

- **Hematopoietic growth factors** (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor [GM-CSF]): Primary prophylactic use of granulocyte-colony stimulating factors is not permitted but they may be used to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guideline.[25] If neutropenic complications are observed in a cycle in which primary prophylaxis with CSFs was not received, secondary prophylaxis may be given at the discretion of the investigator, but only if dose reduction or delay are not considered to be a reasonable alternative.

- **Erythropoietin** may be used at the investigator's discretion for the supportive treatment of anemia.

- **H_2-Receptor Antagonists (H_2RAs)** for symptomatic treatment of gastrointestinal disorder (including, but not limited to famotidine, ranitidine, nizatidine, cimetidine). Based on available data, administration of H_2RA with a staggered dosing regimen (twice daily) does not affect absorption or exposure of palboiclib when palbociclib is taken with food. Before the completion of all required PK samplings, if H_2RA administration is needed**,** the dosing of palbociclib should occur at least 10 hours after the H_2RA evening dose and 2 hours before the H_2RA morning dose.
- **Local antacids** for symptomatic treatment of gastrointestinal disorder (eg, aluminum/calcium hydroxide, aluminum/calcium carbonate, bismuth subsalicylate). Based on available data, administration of local antacids with a staggered dosing regimen does not affect absorption or exposure of palboiclib when palbociclib is taken with food. Before the completion of all required PK samplings, if administration of local antacids is needed, local antacids should be given at least 2 hours before or 2 hours after administration of palbociclib.
- **Acid reducing agents (including PPIs, H_2RAs and local antacids)** can be used for symptomatic treatment of gastrointestinal disorder after the completion of PK evaluations.

5.5. Concomitant Radiotherapy or Surgery

Any concurrent radiotherapy (except palliative radiotherapy as specified below) or cancer-related surgery are prohibited throughout the duration of the active treatment phase of the study. Patients requiring any of these procedures will be discontinued from the study.

Palliative radiotherapy is permitted for the treatment of painful bony lesions provided that the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of palbociclib with radiotherapy, palbociclib treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment 1 week after. For patients with bone involvement, it is suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (eg, lesions at risk for spontaneous micro-fractures or painful lesions). Palliative radiotherapy during the active treatment phase will be considered alternative cancer therapy and will result in censoring of the PFS endpoint. The dates on which palliative radiotherapy is administered should be recorded on the appropriate CRFs.

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and palbociclib required to minimize the risk of impaired wound healing and bleeding has not been determined. Based on the available pharmacokinetic data, stopping palbociclib is recommended at least 7 days prior to elective surgery. Postoperatively, the decision to reinitiate palbociclib treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

All study procedures are described in SCHEDULE OF ACTIVITIES.

6.1. Screening

Voluntary, written, dated, and signed informed consent must be obtained before any study specific procedures are performed (with the exception of certain imaging assessments if meeting the criteria defined in this section); however, it may be obtained more than 28 days before enrollment.

Radiographic tumor assessments (as documented on the Table 3 Tumor Assessment Requirement Flowchart) that were performed before the signing of the informed consent form as routine procedures (but within 28 days prior to study entry) do not need to be repeated and may be used as baseline assessments, as long as:

- The tests were performed per the method requirements outlined in the Tumor Assessment Requirement Flowchart and Section 7.2 Efficacy Assessment.
- Appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.

Bone scans performed as routine procedures within 12 weeks prior to enrollment may also be accepted as baseline assessment if they meet the same requirements listed above.

Brain scans performed as routine procedures within 6 weeks prior to enrollment may also be accepted as baseline assessment if they meet the same requirements listed above.

If screening and Day -1 occur on the same day, the required assessments do not need to be repeated on Day -1.

All lens grading evaluable patients will undergo the following ophthalmic procedures at screening:

- Best corrected distant visual acuity;
- Refractive error associated with best corrected distant visual acuity;
- Intraocular pressure (IOP-one reading);
- Slit lamp biomicroscopy of the anterior segment including cell count and flare grading;
- Lens grading with the Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading Procedures using a laminated reference pocket card (See Appendix 7) - (pupil dilated examination);
- Funduscopy (Ophthalmoscopy – pupils must be dilated).

Patients with ophthalmic conditions (eg, anophthalmus, phthisis, aphakia, pseudophakia) that would prevent grading of the lens in both eyes will not be considered evaluable for this ophthalmic assessment and do not need to undergo these ophthalmic procedures. Reasons for not being evaluable must be clearly documented in the patient source notes.

All ophthalmic examinations will be performed by an ophthalmologist. Refer to 7.3.4 Ocular Safety Assessments for further details on these procedures.

For details on baseline procedures, see the Schedule of Activities tables.

6.1.1. Screen Failure

Patients who completed the informed consent process but do **NOT** meet all eligibility criteria and therefore are **NOT** enrolled to the study will be considered as screen failures.

Clinical sites must provide for all screen failures the following information using the appropriate CRF pages: screening number, demographic data as well as the final subject summary including the reason for screening failure.

6.2. Pharmacokinetics

During the intensive PK collection parts, an indwelling catheter is allowed if there is a need. For blood sampling time points, see SCHEDULE OF ACTIVITIES and Section 7 ASSESSMENTS.

6.3. Active Treatment Phase

For procedures during this phase, see SCHEDULE OF ACTIVITIES and Section 7 ASSESSMENTS.

In the event that the start of a new cycle is delayed due to treatment-related toxicity, procedures required on Day 1 of the given cycle will be performed when palbociclib is resumed. New cycle Day 1 procedures that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated (1) if not required to determine whether study drug may be resumed and (2) if performed within 7 days prior to study drug resumption.

6.4. End of Treatment Visit

If the required assessments are not completed during the previous 4 weeks on study (or within the previous 8 weeks for disease assessments), the assessments will be done at the end of treatment visit. The end of treatment visit will be performed as soon as possible but no later than 4 weeks (ie, 28 days) ± 7 days from last dose of investigational product and prior to the initiation of any new anticancer therapy. Patients who have already demonstrated objective disease progression as per RECIST v.1.1 do not need to have scans repeated at the end of treatment visit.

For details on procedures to be performed at the End of Treatment visit, see the SCHEDULE OF ACTIVITIES tables.

6.5. Patient Withdrawal

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn 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. The reason for discontinuation from treatment will be collected on the appropriate CRF.

Reasons for withdrawal of study treatment may include:

- The patient withdraws consent to undergo further treatment;
- Disease progression as per RECIST v.1.1 (unless there is reasonable evidence of ongoing clinical benefit to justify continuation on protocol according to the investigator after discussion with the sponsor's medical monitor);
- Global deterioration of health status requiring discontinuation without objective evidence of disease progression as per RECIST v.1.1;
- Treatment delay for more than 2 weeks for treatment-related toxicity (unless there is reasonable evidence of ongoing clinical benefit to justify continuation on protocol; this must be discussed with the sponsor);
- Unacceptable toxicity;
- The patient is lost to follow-up;
- Poor compliance with either protocol procedures or with taking the study medications;
- The patient no longer requires treatment (eg, patients having experienced a tumor reduction followed by resection and no longer having evaluable disease);
- Initiation of treatment with another anti-cancer therapy not specified in the protocol;
- Significant protocol violation;
- Study terminated by Sponsor;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. The Investigator should attempt to contact the subject twice. After two attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow up. All attempts to contact the subject and information received during contact attempts must be documented in the subject'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 the patients to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events.

Patient who discontinue from the active treatment phase must have end of treatment/withdrawal evaluations performed as soon as possible but no later than 4 weeks after the last dose of investigational product and prior to initiation of any new anticancer therapy.

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.

If a patient opts to discontinue from the active treatment phase as a result of an unacceptable adverse drug reaction, "withdrawal of consent" should not be the reason for discontinuation. Instead, the reason for discontinuation of active treatment phase, must be recorded as "Unacceptable toxicity" and an appropriate action taken must be assigned on the AE CRF to the adverse event leading to the patient's withdrawal of consent.

7. ASSESSMENTS

All study procedures are detailed in SCHEDULE OF ACTIVITIES.

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 of 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 which he/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.

7.1. Blood Volumes

The highest total blood sampling volume for individual patients from screening to the Lead-in phase and Cycle 1 of the study is approximately 209 mL. The actual collection times of blood sampling may change, but the total blood volume collected will not increase. Blood volume collected in each of the later cycles should be less than the total amount in Lead-in phase plus Cycle 1. Additional blood samples may be taken for safety assessments during the whole study at times specified by the sponsor, provided the total volume taken during the study does not exceed 550 mL during any period of 30 consecutive days.

Table 9. Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times		Total Volume (mL)
		Screening/ Day-1	Lead-in Phase/ Cycle1	
Safety Labs	15	1 or 2	5	105
PK	2		28	56
Blood TK Activity	3	1	15	48
TOTAL				209

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters, if applicable.

7.2. Efficacy Assessments

7.2.1. Tumor Assessment

The importance of timely and complete disease assessments in this study cannot be understated. Disease assessments must be performed as scheduled according to the calendar, regardless of treatment delays resulting from toxicity, to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. A series of incomplete disease assessments will result in censoring of the primary endpoint of PFS back to the time of the last full assessment that did not show progression. Frequent off schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial.

Radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression at the discretion of the investigator. If progressive disease is confirmed per RECIST v.1.1, patients are expected to discontinue study therapy. However, patients may continue the study treatment beyond the time of RECIST-defined progressive disease (PD) at the discretion of the investigator if that is considered to be in the best interest of the patient and as long as no new anticancer treatment is initiated.

Screening/baseline tumor assessment will be carried out within 4 weeks (ie, 28 days of study entry (unless otherwise specified below).

Disease assessment for <u>all patients</u> at baseline will include:

- CT or MRI scan of the chest, abdomen, and pelvis (CAP).
- CT or MRI scan of any other sites of disease as clinically indicated.
- Clinical assessment of superficial disease which will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the CRF.
- Bone scans in order to detect bony sites of disease. Any suspicious abnormalities (ie, hotspots) identified on the bone scans at baseline must be confirmed by X-ray, CT scan with bone windows or MRI. Bone lesions identified at baseline will follow the same assessment schedule as for measurable lesions. Baseline brain CT or MRI are

only required in case signs and symptoms suggest the presence of metastatic brain disease. Refer to Section 6.1 for further details on timing allowance for baseline brain and bone scans.

Post-baseline tumor assessments will be performed every 12 weeks (±7 days) and bone scans (as applicable) every 24 weeks (±7 days) from C1D1 until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anticancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up) whichever occurs first. Imaging assessments are to be scheduled using the C1D1 date as the reference date for all time-points and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST definitions will continue to have tumor assessment performed during the follow-up visits every 12 weeks (±7 days) and bone scans (as applicable) every 24 weeks (±7 days) until documented disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Every effort should be made to perform a last tumor assessment before starting a new anticancer therapy. Additional unscheduled tumor assessments may be performed as clinically indicated at any time.

Post-baseline tumor assessments will include:

- CT or MRI scan of the chest, abdomen, and pelvis (CAP).
- CT or MRI scan of any other sites of disease identified at baseline.
- Clinical assessment of sites of superficial disease identified at baseline. Clinical assessment of superficial disease must coincide with the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the CRF.
- Bone lesions imaging:
    - If bone lesions were identified at baseline the following assessment must be performed:
        - X-ray/CT scan/MRI every 12 weeks (± 7 days) from the date of C1D1 using the same modality used to confirm the bone lesions at baseline. Areas that have received palliative radiotherapy on study cannot be used to assess response to study treatment.

- Bone scans every 24 weeks (± 7 days) from the date of C1D1 and to confirm complete response. Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan, or MRI.

- If no bone lesions were identified at baseline, bone scans should be performed as clinically indicated (ie, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) but are required to confirm complete response. Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan, or MRI.

- Repeat brain scans will be required only if metastases are suspected.

The CT scans, including brain CT scan if applicable, should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease.

However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it must be performed a few days before any treatment that may affect bone-marrow cellularity (eg, G-CSF).

The same method and technique must be used to characterize each lesion identified and reported at baseline, during the study treatment period and during follow-up. The use of plain-film X-rays (with the exception of bone X-rays as detailed above) is discouraged. The use of positron emission tomography (PET) imaging as the only imaging modality is not permitted.

For patients having effusions or ascites, cases having cytological proof of malignancy should be recorded as non-target lesions on the tumor assessment CRFs. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the non-target lesion CRF.

Objective tumor response will be measured using the Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1, see http://www.eortc.be/recist/default.htm). Also please refer to Appendix 2. All measurements should be recorded in metric notation using a ruler or calipers.

For patients with bone-only disease:

- Treatment outcome will be recorded in the CRF as complete response (CR), stable disease (SD) or progression (PD).

Interpretation will be PD if:

- The malignant nature of one or more new lesions identified with bone scan is confirmed with X-ray, or CT, or MRI scan,
- Flare observed in bone scan is followed by confirmation of progression with other imaging modalities,
- Clinical worsening of the disease is assessed by bone scan and disease progression (ie, new lesion(s)) is confirmed with other imaging modalities.
- Unequivocal progression of existing bone lesions.

Interpretation will be SD if:

- The malignant nature of all the new lesions identified with bone scan is not confirmed.

In the following cases the patient will be censored at the date of prior tumor assessment with no PD: 1) on-study fracture; 2) on-study management of pain (palliative radiation therapy, palliative surgery), 3) clinical worsening not objectively confirmed; 4) on-study change of therapy. In all the censored cases (no objectively documented PD) tumor assessment will be performed until PD. Also, it will be at the discretion of the investigator to discontinue the study treatment.

It is suggested to institute palliative radiotherapy (eg, lesions at risk for spontaneous micro-fractures or painful lesions) before study initiation as well as palliative surgery if possible and clinically appropriate.

7.3. Safety Assessments

7.3.1. Adverse Events

Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0, see Appendix 3 National Cancer Institute (NCI) common Terminology Criteria for Adverse Events (CTCAE)), timing, seriousness, and relatedness; and laboratory abnormalities.

Baseline tumor-related signs and symptoms will be recorded prior to study entry and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

7.3.2. Laboratory Safety Assessments

Blood tests include:

- Hematology: white blood cell count, platelet count, hemoglobin (Hb), and white blood cell differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes).

- Blood chemistry: Aspartate aminotransferase (AST) / alanine aminotransferase (ALT), alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, BUN (or urea), serum creatinine, albumin, fasting lipid panel (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL] and triglycerides), hemoglobin A1c (HgbA1c), fasting glucose and fasting insulin.

- Coagulation: PT or INR, PTT or aPTT. Additional coagulation studies may be performed as clinically indicated.

- Hbs Ag, anti-HCV, HIV tests

Hematology and blood chemistry will be drawn at the time points described in SCHEDULE OF ACTIVITIES and analyzed at local laboratories, except HgbA1c, fasting lipid panel, fasting glucose and fasting insulin that will be analyzed at a central laboratory designated by the Sponsor.

Hematology assessments will be conducted regardless of food intake. HgbA1c assessments will be conducted regardless of food intake; fasting glucose, fasting insulin and fasting lipid panel will be assessed following an overnight fast (at least 10 hours); samples for other blood chemisty tests should be collected following at least a 4-hour fast. Therefore, when all of these assessments are conducted together, they should be done before food intake. Additional hematology/chemistry panels may be performed at the discretion of investigators as clinically indicated for planning treatment administration, dose modification, or further evaluation of adverse events.

Urinalysis will include protein and blood. Dipstick is acceptable. If positive, collect 24-hr urine (for protein excretion) and perform microscopic analysis of the urine.

7.3.3. Electrocardiogram (ECG)

Electrocardiograms (ECGs) should be collected at pre-dose on the days specified in the Study Procedures section of this protocol. ECG measurements will include PR interval, QT interval, RR interval, and QRS complex. Heart rate should be measured and recorded as well. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. Additional ECGs may be performed as clinically indicated.

12-lead triplicate ECGs monitoring will be undertaken in all patients enrolled in the trial. At each time point (see SCHEDULE OF ACTIVITIES and Table 1), 3 consecutive ECGs will be performed approximately 2 minutes apart to determine the mean QTc interval. All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position. When the ECG schedule is matched with PK sampling, ECG must be carried out before PK sample drawing such that the PK samples are collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). ECG evaluation should be conducted before food intake.

If the mean QTc interval is prolonged (>500 msec), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including

verification that the machine reading is accurate. If the prolonged mean QTc is confirmed, immediate search for reversible causes (including electrolyte abnormalities, hypoxia, and concomitant medications for drugs with the potential to prolong the QT interval) should be performed by investigator and sponsor. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc falls below 501 msec.

- If QTc interval reverts to less than 501 msec, and in the judgment of investigator(s) in consultation with the sponsor the cause is determined to be other than study drug, treatment may be continued with regular ECG monitoring under hospital supervision.

- If in that timeframe the QTc intervals remain above 501 msec the study drug will be held until the QTc interval decreases to <501 msec.

Prior to concluding that an episode of QTc prolongation is due to study drug, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by a specialist.

If investigational product causality cannot be ruled out, investigational product dose adjustment and/or discontinuation should be performed according to instructions provided in 5.2.4 Recommeded Dose Modification. Additional triplicate ECGs may be performed as clinically indicated.

7.3.4. Ocular Safety Assessments

Ocular assessments will be performed at the time points described in SCHEDULE OF ACTIVITIES by ophthalmologists.

7.3.4.1. Visual Acuity and Refraction

Visual acuity will be assessed by using a standard wall or projection chart before implementing any procedures that can affect vision (eg, pupil dilation, tonometry, and gonioscopy). Snellen notation and other methods are allowed to be used and the method being used should be indicated on the CRF pages. The original results should be recorded with the respective units (meter or feet, or left blank for fraction number) on the CRF pages. Conversion to Snellen notation will not be needed.

The same optotype will be used throughout the study for a specific patient, and the right eye should be tested first. The refractive error will be determined at the Screening visit. The examiner should ensure that patients are seated comfortably and that they do not move their head forward or backward during testing. Patients will be told that the chart contains only letters.

The line read with 2 or fewer errors will be recorded. If 3 of the 5 letters on a line are read correctly, the patient will be given credit for that line. For example, if the patient reads 20/25 +3, 20/20 will be recorded.

A decrease in best-corrected visual acuity of 3 lines or more from the Screening visit will be reported as an adverse event. An adverse event of visual acuity will be counted from the following lines: 20/20 or better, 20/25, 20/30, 20/40, 20/50, 20/60, 20/70, 20/80, 20/100, 20/125, 20/150, and 20/200. If the acuity at screening is better than 20/20, the decrease will be calculated from 20/20.

In the event of a decrease in visual acuity of 3 lines or more from screening, refraction will be rechecked at all subsequent study visits. A change in refraction power (spherical or cylindrical) of +/– 1.25 diopters compared with the screening examination will be reported as an adverse event.

7.3.4.2. Intraocular Pressure Measurement

Intraocular pressure (IOP) will be measured using a calibrated Goldmann applanation tonometer or a non-contact method (puff) with the Tonopen, Schiotz or Rebound tonometer. IOP data may be pooled together for analysis. Both eyes will be tested, with the right eye preceding the left eye. The operator will initially set the dial at 10 mm Hg, then look through the slit lamp and adjust the dial to take the reading, and then record the results, including the time assessment is made.

Any IOP increase of greater than 10 mmHg above baseline or any IOP that increases above 25 mm Hg will be reported as an adverse event (AE).

7.3.4.3. Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy with fluorescein will be performed. At each scheduled visit, deposition of pigment on the corneal endothelial layer or the lens capsule or any abnormalities of the lids, conjunctivae, cornea, anterior chamber, iris, or lens (see Lens Grading) will be graded as mild, moderate, or severe. Slit-lamp biomicroscopy should precede IOP measurement and the administration of any pupil-dilating agent for ophthalmoscopy.

Cells and flare in the anterior chamber should be noted during the slit-lamp examination.

Intraocular Inflammation Grading Scale for Biomicroscopy:

	Grade				
	0	1	2	3	4
Grading of aqueous flare[a]	Completely Absent	Barely Detectable	Moderate (iris and lens details clear)	Marked (iris and lens details hazy)	Intense (formed fibrin in aqueous)
Grading of cells in the aqueous[a,b]	No cells	1 to 5 cells	6 to 10 cells	11 to 20 cells	>20 cells

[a] Evaluation of Anterior Chamber Inflammation:

1. Examination of the anterior chamber for cells must be performed before either dilation or applanation tonometry.
2. The light intensity of the slit lamp is turned to the maximum tolerated by the patient.
3. High magnification and 1 x 2 mm slit are used.

4. The ray of light as directed at an angle of approximately 45° to the plane of the iris.

[b] Modified from Hogan et al. 1959.[26]

During the study, any new finding or deterioration from baseline findings should be reported as an adverse event.

7.3.4.4. Lens Grading

When doing lens grading, graders must be aware of their bias, either conscious or unconscious, that cataract is a unidirectional disease that steadily gets worse with age. Because of this bias, if one knows the baseline or any prior lens grade, it is likely that the grade assigned at a follow-up visit will be higher. To avoid this potential observation bias, the grader will remain masked to earlier lens grading and should always start with a blank case report form (CRF). The Wisconsin AREDS 2008 Clinical Lens Opacity Grading Procedure will be used.[27] Once the pupils are dilated to at least 5 mm, use slit lamp with ~10X magnification and brightest beam intensity.

- Nuclear opacity
  - Orient beam at 45° to viewing axis
  - Adjust slit beam to standard parameters: 8 mm height and 0.3 mm width
  - Compare opalescence of nucleus with those on the provided pocket card of standard photos
- Cortical and Posterior Subcapsular Cataract (PSC) opacities
  - Select wide slit beam setting optimum for retro-illumination of lens
  - Visualize lens opacities against red fundus reflex background
  - Count only opacities definitely visible against red reflex
  - Mentally combine all cortical opacities into one contiguous area
  - Compare total opacity area with those on the provided pocket card of standard photos
- Grade each type of opacity in half steps from <1 to >3 (1=mild, 2=moderate and 3=severe) using the scale defined on the provided pocket card of standard photos

7.3.4.5. Funduscopy (Ophthalmoscopy)

Funduscopy (Ophthalmoscopy) will be performed after dilation of the pupils to examine the vitreous body, retina, and optic nerve head. At screening, any abnormalities and pathologic findings will be graded as mild, moderate, or severe.

Any new findings or deterioration from baseline findings will be reported as an adverse event.

7.3.5. Other Safety Assessments

A full physical examination including an examination of all major body systems, height (at screening only), weight, blood pressure and pulse rate which may be performed by a physician, registered nurse or other qualified health care provider, will be required at screening, Day -1, Day 1 of Cycles 1 and 2, and at the end of treatment.

Symptom directed physical examinations, blood pressure and pulse rate will be performed at subsequent visits.

Performance Status: The Eastern Cooperative Oncology Group (ECOG) performance status scale will be used (see Appendix 4).

7.4. Pharmacokinetic Assessments

Blood samples will be collected for intensive PK assessments of palbociclib during the single-dose PK part in Lead-in phase and multiple-dose PK part in Cycle 1 as outlined in the SCHEDULE OF ACTIVITIES. Sparse PK samples will be collected for determination of letrozole concentration at predose in Cycles 1 and 2 as outlined in the SCHEDULE OF ACTIVITIES. Additional blood samples may be collected at discretion of investigators.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. The actual time of the sample collection and the most recent dosing time both prior to and after each sample collection will be recorded in the CRF. For instance, dosing times on both Cycle 1 Day 18 and Day 19 should be recorded for PK sample collection on Day 19; dosing times of letrozole on both Cycle 1 Day 28 and Cycle 2 Day 1 should be recorded for PK sample collection of letrozole on Cycle 2 Day 1. In case that the samples have to be collected in a later cycle, the same rule should be applied. The date of any missed doses should also be recorded in the CRF.

PK sample collections scheduled at steady state after multiple dosing of palbociclib should be conducted given that there is no dosing interruption for at least 8 days prior to sample collection. If the sample collection is missed for any reason or if the PK data collected are deemed not evaluable by the Sponsor, the PK sample collection may be repeated during a later cycle. Patients must be instructed to withhold their daily dose of study drugs on PK sampling days until safety assessments (ie, hematology, blood chemistry, and ECGs) and pre-dose PK sample collection have been completed. It is always recommended that self-administration of study drugs should occur in the morning, especially on Days 18, 19, 20 and 28 of Cycle 1 when pre-dose PK samples will be taken on the next day, to ensure pre-dose PK samples are collected at least 20 hours after the previous dose and immediately before the next dose.

PK blood samples will be assayed for palbociclib and letrozole using a validated analytical method in compliance with Pfizer standard operating procedures.

7.4.1. Plasma for Analysis of Palbociclib (PD-0332991)

During all study periods, blood samples (2 mL) to provide a minimum of 0.5 mL plasma for pharmacokinetic analysis will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the STUDY PROCEDURES section of the protocol.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. Predose samples should be obtained immediately prior to the morning dose (within 15 minutes prior to dosing). On these days, administration of palbociclib and letrozole should occur in the CRU to ensure the pre-dose PK samples can be collected, so during the outpatient visits on Days 1, 19 and 20 in Cycle 1 and Day 1 in Cycle 2, patients should be instructed to bring the drug supply and administer the drugs in the CRU after completion of PK collection on that day.

For PK collections scheduled before 24 hours post-dose in CRU, deviation of required collection time within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) from dosing will not be captured as a protocol deviation, as long as the actual collection time is recorded. For samples scheduled after 24 hours post-dose, collections obtained within 10% of the sampling interval (ie, 24 hours in this study) will not be captured as a protocol deviation as long as the actual collection time is recorded. For the PK samples collected during outpatient visits, deviation of required collection time larger than 10% of sampling interval (ie, 24 hours in this study) may be acceptable as long as the actual collection time is recorded.

- Samples will be centrifuged at approximately 1700 x g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C within 1 hour of collection.

- Samples will be analyzed for palbociclib (PD-0332991) using a validated analytical method in compliance with Pfizer standard operating procedures.

[redacted]

Refer to the Laboratory Manual for detailed collection, processing and shipping procedures.

7.4.2. Plasma for Analysis of Letrozole

During all study periods, blood samples (2 mL) to provide a minimum of 0.5 mL plasma for pharmacokinetic analysis will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the STUDY PROCEDURES section of the protocol.

The actual times may change but the number of samples will remain the same. All effortswill be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). Predose samples should be obtained immediately prior to the morning dose.

- Samples will be centrifuged at approximately 1700 x g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C within 1 hour of collection.

- Samples will be analyzed for letrozole using a validated analytical method in compliance with Pfizer standard operating procedures.

[redacted]

Refer to the Laboratory Manual for detailed collection, processing and shipping procedures.

7.4.3. Shipment of Pharmacokinetic Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

7.5. Biomarker Assessments

Skin biopsy tissues and blood samples will be collected for biomarker assessments of palbociclib at pre-dose and during the single and multiple dose PK parts as described in SCHEDULE OF ACTIVITIES. All the biomarker samplings are scheduled at the same time with some of the PK samplings. All efforts should be made to coordinate biomarker sample collections immediately after the completion of PK samplings with the actual PK collection time being the closest to the nominal times. If PK samplings scheduled at steady state are conducted in a later cycle for any reason, samples for biomarker assessments should be also collected at the same time to ensure the collections are time-matched between PK and biomarker. The actual time of the sample collections will be recorded on the source documents and CRF.

7.5.1. Skin Biopsy

Skin punch biopsy tissues are required from enrolled patients for biomarker assessments (pRb and Ki67) and will be collected on the planned days described in SCHEDULE OF ACTIVITIES. In order to avoid intensive collections, patients will be randomized into 2 groups associated with different schedules in Lead-in phase and Cycle 1, as indicated in the

footnote of SCHEDULE OF ACTIVITIES. Whenever possible, all efforts should be made to conduct skin tissue collection within 30 minutes after the completion of PK samplings.

Biopsy at areas with colored (pigmented) skin contour should be avoided. Skin biopsy is rarely contraindicated. Precautions should be taken if a patient has a history of an allergy to local or topical anesthetics, and other materials to be used for biopsy procedure, or has evidence of an active infection at the biopsy site. Prebiopsy evaluation should also include a history for any bleeding disorders, coagulopathy, and medications that might affect hemostasis through their anticoagulative effects, or prior history of bleeding problems after a surgery or procedure, which may indicate an intrinsic clotting factor deficiency. Such factors do not preclude skin biopsy, but may prolong or complicate hemostasis. In some rare conditions, keloid might develop, especially for patients who have history of disseminated keloid. Most complications of skin biopsy, if would develop, are minor and temporary. If the patient experience severe bruising, tenderness, infection or uncontrolled bleeding as well as related conditions noted by investigators after conducting the procedure, investigators should report to the sponsor immediately. Based on medical discretion and discussion with sponsor, if the patient is considered as inappropriate to continue the skin biopsy procedure, investigators could consider withholding temporarily or cancelling the following scheduled biopsies.

Retrospective testing of formalin fixed paraffin embedded (FFPE) tissue samples for pRb and Ki67 expression will be performed in a central laboratory designated by the sponsor. Results from this assay will be used for exploratory analyses between PK and pharmacodynamics markers.

Detailed information about biomarker sample collection, preparation, storage, labeling, and shipment is indicated in the Laboratory Manual.

7.5.2. Thymidine Kinase Blood Test

Blood samples (3 mL) to provide a minimum of 1 mL serum will be collected from all the enrolled patients into appropriately labeled tubes for assessments of thymidine kinase (TK) activity at time points described in SCHEDULE OF ACTIVITIES. All the sample collections for TK analysis should occur immediately after the completion of PK samplings without performing venipuncture again at the same time point. TK samples collected within 15 minutes after the completion of PK samplings will be considered as protocol compliant.

Retrospective testing of serum samples for TK activity will be performed in a central laboratory designated by the sponsor. Results from this testing will be used for exploratory analysis between PK and pharmacodynamics markers.

Detailed information about biomarker sample collection, preparation, storage, labeling, and shipment is indicated in the Laboratory Manual.

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 information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an 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 non-serious adverse event 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 subject provides informed consent, which is obtained prior to the subject'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. Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events 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 non-serious) should be recorded on the CRF from the time the patient has taken at least one dose of investigational product through last patient visit.

- If a patient begins a new anticancer therapy, the AE reporting period for non-serious 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. 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 (outside of protocol-stipulated dose adjustments) 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.

8.5. Serious Adverse Events

A Serious Adverse Event (SAE) 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 CTCAE Grade 5 (see Section on Severity Assessment).

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.

8.5.1. 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 Section 8.13.1 SAE Reporting Requirements).

8.5.2. 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 (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available.

- For patients with preexisting ALT OR AST OR total bilirubin values above the upper limit of normal, 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 X ULN, or ≥8 X 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 X ULN or if the value reaches ≥3 X 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-glutamyl transferase, prothrombin time (PT)/international normalized ration (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and 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 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 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.

8.6. 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 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 an 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 preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab 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;
- Pre-planned treatments or surgical procedures 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 non-invasive 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.

8.7. Severity Assessment

As required on the adverse event case report forms, the investigator will report adverse events using concise medical terminology (verbatim) and use the following definition of severity in accordance with the Common Terminology Criteria (CTCAE) term for Adverse Events (Version 4.0, http://ctep.cancer.gov/reporting/ctc.html) to describe the maximum intensity of the adverse event.

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.0 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 patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse 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 Section 8.13 on Reporting Requirements). 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.

8.9. Exposure During Pregnancy

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

- 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;

  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).

- 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 a Serious Adverse Event Report Form and an Exposure in Utero (EIU) 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 EIU 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 EIU 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 EIU 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 pre-procedure 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 serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the investigational product

Additional information regarding the exposure during pregnancy 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). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.10. Occupational Exposure

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

An occupational exposure is reported to the drug safety unit within 24 hours of 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 Case Report Form (CRF), however a copy of the completed SAE Report form is maintained in the investigator site file.

8.11. Withdrawal Due to Adverse Events (See Also Section 6.5 Patient Withdrawal)

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.

8.12. Eliciting Adverse Event Information

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

8.13. 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.

8.13.1. 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 timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, 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/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes 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.

8.13.2. Non-Serious 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.

8.13.3. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event 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, 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

A minimum of approximately 25 patients will be enrolled to the study and this sample size was selected to satisfy regulatory requirement by CFDA in terms of PK evaluation in Chinese population and provide meaningful data for secondary endpoint analysis. Patients

may be replaced if there are less than 12 patients completing the single-dose and multiple-dose PK sample collections without dosing interruption or dose modification.

9.2. Analysis of Pharmacokinetics

9.2.1. Analysis Populations

The PK concentration population is defined as all patients enrolled and treated who have at least 1 PK concentration in the single-dose and/or multiple-dose PK part.

The PK parameter analysis population is defined as all patients enrolled and treated who have at least 1 of the PK parameters of primary interest in the single-dose and/or multiple-dose PK part.

The PK evaluable analysis set is defined as all patients in the PK parameter analysis set who complete both the single dose PK and multiple dose PK parts without major protocol deviations.

9.2.2. Derivation of Pharmacokinetic Parameters Prior to Analysis

PK parameters of palbociclib following single dose administration will be derived from the concentration-time profiles as shown in the table below.

Parameter	Definition	Method of Determination
AUC_{10}	Area under the plasma concentration versus time curve from time zero to the time 10 hours	Linear/Log trapezoidal method
AUC_{24} (=$AUC_{sd,\tau}$)	Area under the plasma concentration versus time curve from time zero to the time 24 hours (= a dosing interval of τ)	Linear/Log trapezoidal method
AUC_{last}	Area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}	Area under the plasma concentration versus time curve from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}/k_{el})$, where C_{last} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis; k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
C_{max}	Maximum plasma concentration	Observe directly from data

T_{max}	Time for C_{max}	Observe directly from data as time of first occurrence
CL/F	Apparent oral clearance	Dose/AUC_{inf}
$t_{½}$	Terminal plasma half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
MRT	Mean residence time	$AUMC_{inf}/AUC_{inf}$, where $AUMC_{inf}$ is area under the first moment curve from zero time to infinity.
Vz/F	Apparent volume of distribution	Dose/ (AUC_{inf} *k_{el})
k_{el}	Rate constant for terminal phase	Calculated by a linear regression of the log-linear concentration-time curve

PK parameters of palbociclib following multiple dose administration will be derived from the concentration-time profiles as shown in the table below.

Parameter	**Definition**	**Method of Determination**
$AUC_{ss,\tau}$	Area under the plasma concentration versus time curve within a dosing interval of τ (=24 hr) at steady state	Linear/Log trapezoidal method
$C_{ss,max}$	Maximum plasma concentration at steady state	Observe directly from data
$C_{ss,min}$	Minimum plasma concentration at steady state	Observe directly from data
$C_{ss,av}$	Average plasma concentration at steady state	$C_{ss,av}= AUC_{ss,\tau} / \tau$
$T_{ss,max}$	Time for $C_{ss,max}$	Observe directly from data as time of first occurrence within τ at steady state
CL/F	Apparent clearance	Dose/ $AUC_{ss,\tau}$
Vz/F	Apparent volume of distribution	Dose/ ($AUC_{ss,\tau}$*k_{el})
$t_{½}$	Terminal half-life	ln (2)/k_{el}, Where k_{el} is the terminal phase rate constant following MD calculated by a linear regression of the log-linear concentration-time curve.

PTF (DF)	Peak to trough fluctuation at steady state (= DF)	$(C_{ss,max}-C_{ss,min})/C_{ss,av}$
R_{ac}	Observed accumulation ratio	$R_{ac}=AUC_{ss,\tau}/AUC_{sd,\tau}$, where $AUC_{sd,\tau}$ is AUC_{24}
R_{ss}	Steady-state accumulation ratio	$R_{ss}=AUC_{ss,\tau}/AUC_{inf}$, where AUC_{inf} is from single dose.

Actual PK sampling times will be used in the derivation of PK parameters.

Summary of pharmacokinetic parameters will be for PK parameter analysis set and PK evaluable analysis set. The PK parameters AUC_{10}, AUC_{24}, AUC_{last}, AUC_{inf}, C_{max}, T_{max}, CL/F, $t_{1/2}$, MRT, Vz/F and K_{el} of palbociclib following single dose administration of palbociclib will be listed and summarized descriptively for Lead-in phase. The PK parameters $AUC_{ss,\tau}$,$C_{ss,max}$, $C_{ss,min}$, $C_{ss,av}$, $T_{ss,max}$, CL/F, Vz/F, $t_{1/2}$, PTF, R_{ac}, and R_{ss} of palbociclib following multiple dose oral administration of palbociclib will be listed and summarized descriptively.

The plasma concentration data for palbociclib and letrozole will be listed and summarized descriptively by day and nominal PK sampling time for subjects in the PK concentration analysis set. Overlay multiple patient profiles of the plasma concentration-time data for palbociclib will be plotted using actual PK sampling time (separate plots for single and multiple dose PK). For mean and median plots of palbociclib plasma concentration-time, the nominal PK sampling time will be used. Mean and median profiles will be presented on both linear-linear and log-linear scales. For individual patient plots of palbociclib, the actual PK sampling time will be used, while the predose time will be set to zero.

The trough plasma concentration of palbociclib on Days 19-21 in Cycle 1 will also be plotted for visual inspection of steady-state condition. The trough plasma concentration of letrozole on Days 19-21 and Cycle 2 Day 1 will also be plotted for visual inspection of multiple dose level.

9.3. Efficacy Analysis

The efficacy analysis set is defined as all enrolled patients who start the treatment of Cycle 1. The analysis of efficacy endpoints dependent on disease assessment (PFS, DC, OR and DR) will be based on investigator assessment of disease response and progression.

Censoring for time-to-event endpoints will be detailed in the SAP.

Progression-free survival (PFS)

Progression-free survival is the time from C1D1 to date of first documentation of disease progression or death due to any cause, whichever occurs first. Documentation of progression must be by objective disease assessment as defined by the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). PFS data will be censored on the date of the last tumor assessment on study for patients who do not have objective tumor progression and who do

not die while on study. Additionally, patients who start a new anti-cancer therapy prior to documented disease progression will be censored at the date of the last tumor assessment prior to the start of the new therapy.

PFS will be summarized in the efficacy analysis set using the Kaplan-Meier method and displayed graphically. Median event time and 95% confidence interval for the median will be provided.

Objective Response (OR)

Objective response is defined as a complete response (CR) or partial response (PR) according to the RECIST recorded from C1D1 until disease progression or death due to any cause.

A patient will be considered to have achieved an OR if the patient has a sustained complete response (CR) or partial response (PR) according to RECIST v.1.1 definitions. Otherwise, the patient will be considered as non-responders in the OR rate analysis. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the OR rate analysis.

The OR rate (ORR) will be estimated by dividing the number of patients with objective response (CR or PR) by the number of patients in the efficacy analysis set ("response rate"). A 95% confidence interval (CI) will be provided for the ORR.

In addition, the best overall response for each patient will be summarized.

Disease Control (DC)

Disease control (DC) is defined as complete response (CR), partial response (PR), or stable disease (SD) ≥24 weeks according to RECIST version 1.1 recorded in the time period between C1D1 and disease progression or death due to any cause.

The DC rate (DCR) will be estimated by dividing the number of patients with CR, PR, or SD ≥24 weeks by the number of patients in the efficacy analysis set. A 95% CI for the DCR will be provided.

Duration of Response (DR)

For patients with an objective response (CR or PR), duration of response (DR) is the time from first documentation of CR or PR to date of first documentation of objective progression or death. Date of first documentation of PD and date of first documentation of CR or PR will be based on investigator assessment of response. DR data will be censored on the date of the last tumor assessment on study for patients who do not have objective tumor progression and who do not die due to any cause while on study. DR will only be calculated for the subgroup of patients with an objective response.

DR will be summarized in the efficacy analysis set using the Kaplan-Meier method and displayed graphically. Median event time and 95% confidence interval for the median will be provided.

1-year PFS Probability

The 1-year PFS probability will be estimated using the Kaplan-Meier method and a 2-sided 95% CI for the log [-log(1 year PFS probability)] will be calculated using a normal approximation, and then back transformed to give a CI for the 1-year PFS probability itself.

9.4. Analysis of Other Endpoints

Descriptive statistics will be used to summarize all patient characteristics, treatment administration/compliance, prior and concomitant medications and non-drug treatments, and biomarkers. Data will also be displayed graphically, where appropriate.

In addition, the relationship between exposure, biomarker expression, efficacy/safty endpoints will be explored if emerging data allows. The results of these exploratory analyses may be reported separately from the clinical study report.

9.5. Safety Analysis

The safety analysis set includes all enrolled patients who receive at least one dose of study medication.

Adverse events, ECGs, blood pressure, pulse rate, continuous cardiac monitoring, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of patients. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern as defined will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination, including neurologic examination, information collected during the course of the study will be captured for inclusion into the study database, unless otherwise noted. Any untoward findings identified on physical and/or neurologic examinations conducted after the administration of the first dose of study medication will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that is used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs will be considered source data and included into the study database. Demographic data collected at Screening will be included in the study database.

9.5.1. Analysis of Adverse Events and Laboratory Abnormalities

Adverse Events (AEs) will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment-Emergent Adverse Events (TEAEs), those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, serious AE (SAE), treatment-related AE, and treatment-related SAE

will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles >1) as well as by relatedness to trial treatment.

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay based on the NCI CTCAE v4.0 severity grade. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles >1). For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal or not done.

9.5.2. Ocular Events

Ocular events will be reported as part of the adverse event analysis described above. Additionally, changes in lens grading while on study treatment will be analyzed as described in the Statistical Analysis Plan.

9.5.3. Analysis of Electrocardiogram Measurements

All ECGs obtained during the study will be evaluated for safety. The average of the triplicate ECG measurements will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates.

If any of the three individual ECG tracings has a QTc interval >500 msec, but the mean of the triplicates is not >500 msec, the data from the subject's individual tracing will be described in a safety section of the study report in order to place the >500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change of QTc post dose from the average of the pre-dose triplicate values.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Bazett's, Fridericia's and possibly a study specific factor). Data will be summarized and listed for QT, HR, RR, PR, QRS and QTc by time. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTc value and changes from baseline in QTc after treatment by day and time point. For each patient, the maximum change from baseline will be calculated as well as the maximum post-baseline value across time points. Categorical analysis of the QTc data will be conducted and summarized as follows:

The number of patients with maximum change from baseline in QTc (<30, 30-59, and ≥60 msec);

The number of patients with maximum post-dose (post-baseline) QTc (<450, 450-<480, 480-≤500, and >500 msec).

9.6. Data Monitoring Committee

This study will not use a Data Monitoring Committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits for studies conducted outside of Pfizer Clinical Research Units 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 is 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.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), 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.

For studies conducted outside of the Pfizer Clinical Research Units, 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 is true. Any corrections to entries made in the CRFs, 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 source documents. In these cases, a document should be available at the investigator’s 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, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), 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 to 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 (IRB)/Independent Ethics Committee (IEC)

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/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC 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 Patients (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. Subject Information and Consent

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

Patient names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the study patient. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

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

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legal representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document. The patient will be provided with a copy of the signed informed consent form.

12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

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 which 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 that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of Trial in all participating countries is defined as the time which:

- Enrollment is completed and;
- Assessments and requirements up to 28 days after permanent discontinuation of treatment of the last patient are completed as per protocol and all data are submitted for all patients.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug 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 7 days. 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. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) 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, 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 (other than the study results themselves) before disclosure.

If the Study is part of a multi-centre study, the investigator agrees that the first publication is to be a joint publication covering all centers. 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, patient to the other requirements of this section.

For all publications relating to the study, 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 Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

1. GLOBALCAN 2008 CANCER FACT SHEET

2. Wood WC, Muss HB, Solin LJ, Olopade OI. Malignant Tumors of the Breast. In: De Vita VT Jr, Hellmann S, Rosenberg SA, editors. Cancer, Principle and Practice of Oncology, 7th Edition, Lippincott Williams and Wilkins; 2005; 1415-77.

3. Weinberg, RA. The retinoblastoma protein and cell cycle control. Cell 1995; 81:323-30.

4. Sekido Y, Fong KM, Minna JD. Molecular biology of lung cancer. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer: Principles & Practice of Oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins;2001:917-25.

5. Kaye FJ. RB and cylin dependent kinase pathways: Defining a distinction between RB and p16 loss in lung cancer. Oncogene 2002;21:6908-14.

6. Arguello, F., et al., Flavopiridol induces apoptosis of normal lymphoid cells, causes immunosuppression, and has potent antitumor activity In vivo against human leukemia and lymphoma xenografts. Blood, 1998. **91**(7): p. 2482-90.

7. Bartkova, J., et al., Deregulation of the RB pathway in human testicular germ cell tumours. J Pathol, 2003. **200**(2): p. 149-56.

8. Fink, J.R. and T.W. LeBien, Novel expression of cyclin-dependent kinase inhibitors in human B-cell precursors. Exp Hematol, 2001. **29**(4): p. 490-8.

9. CSR A5481001. A phase 1 clinical, pharmacokinetic, and pharmacodynamic evaluation of 2 schedules of oral PD 0332991, a cyclin-dependent kinase inhibitor, in patients with advanced cancer. 26 March 2009.

10. CSR A5481002. A pilot study of PD 0332991 in patients with previously treated mantle cell lymphoma. 12 September 2006.

11. CSR A5481003. Phase ½, open-label, randomized study of the safety, efficacy, and pharmacokinetics of letrozole plus PD 0332991 (oral CDK 4/6 inhibitor) and letrozole single agent for the first-line treatment of ER positive, Her2 negative advanced breast cancer in postmenopausal women. 02 May 2014.

12. CSR A5481011. A Phase 1 open-label single-radiolabeled dose study to investigate the absorption, metabolism, and excretion of [^{14}C]-PD-0332991 in healthy male volunteers. 09 April 2014.

13. CSR A5481012. A Phase 1 randomized, open-label, 2-sequence, 2-period crossover study of the effect of multiple doses of PD-0332991 on midazolam pharmacokinetics in healthy women of non-childbearing potential. 11 July 2013.

14. CSR A5481017. A Phase 1, open-label, fixed-sequence 2-period study to investigate the effect of multiple doses of rifampin on palbociclib (PD-0332991) pharmacokinetics in healthy volunteers. 21 April 2014.

15. CSR A5481016. A Phase 1, open-label, fixed-sequence 2-period study to investigate the effect of multiple doses of itraconazole on the single dose pharmacokinetics of palbociclib (PD-0332991) in healthy volunteers. 26 September 2014.

16. CSR A5481021. A Phase 1, open-label, 4 sequene 4 period cross-over study of palbociclib (PD-0332991) in healthy volunteers to estimate the effect of food on the bioavailability of palbociclib. 23 April 2014.

17. CSR A5481036. A Phase 1, open-label 6-sequence 3-period crossover study of palbociclib (PD-0332991) in healthy volunteers to estimate the relative bioavailability of palbociclib formulations. 30 April 2014.

18. CSR A5481038. A Phase 1, open-label, 3-period study of the effect of an antacid, a proton pump inhibitor and an H_2-receptor antagonist on palbociclib (PD-0332991) bioavailability under fed conditions in healthy volunteers. 15 Augest 2014.

19. CSR A5481018. A Phase 1, open-label, fixed-sequence 2-period crossover study of palbociclib in healthy subjects to investigate the potential effect of antacid treatment on the pharmacokinetics of a single oral dose administered under fasted conditions. 25 April 2014.

20. Investigator's Brochure, A548 (Palbociclib, PD-0332991). December 2013.

21. PMAR-EQDD-A548b-DP4-287. Palbociclib QTc-concentration analysis in cancer patients. 24 April 2014.

22. Elhajouji A, Van Hummelen P, Kirsch-Volders M. Indications for a threshold of chemically-induced aneuploidy in vitro in human lymphocytes. Environmental and Molecular Mutagenesis 1995; 26(4): 292-304.

23. Parry JM, Fielder RJ, McDonald A. Thresholds for aneuploidy-inducing chemicals. Mutagenesis 1994; 9(6): 503-4.

24. Bentley KS, Kirkland D, Murphy M, et al. Evaluation of thresholds for benomyl- and carbendazim-induced aneuploidy in cultured human lymphocytes using fluorescence in situ hybridization. Mutation Research 2000; 464(1): 41-51.

25. Smith TJ, Khatcheressian J, Lyman GH,et al. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. Journal of Clinical Oncology 2006; 24, 19: 3187-205.

26. Hogan MJ, Kimura SJ, Thygeson P: Signs and symptoms of uveitis: I. Anterior uveitis. Am J Ophthalmol 1959; 47:155-70.

27. Chew EY, Kim J, Sperduto RD, Datiles MB 3rd, Coleman HR, Thompson DJ, Milton RC, Clayton JA, Hubbard LD, Danis RP, Ferris FL 3rd. Evaluation of the age-related eye disease study clinical lens grading system AREDS report No. 31. Ophthalmology. 2010 Nov;117(11):2112-9.

28. Okada Y, Hirota T, Kamatani Y,et al. Identification of Nine Novel Loci Associated with White Blood Cell Subtype in a Japanese Population. PLoS Genet 2011; 7(6): 1-10.

Appendix 1. Abbreviations

ABC	Advanced Breast Cancer
ASCO	American Society of Clinical Oncology
AE	Adverse Event
AI	Aromatase Inhibitor
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferases
ANC	Absolute Neutrophil Count
AUC_{10}	Area under the plasma concentration versus time curve from time zero to the time 10 hours
AUC_{24}	Area under the plasma concentration versus time curve from time zero to the time 24 hours
AUC_{last}	Area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration (C_{last})
AUC_{inf}	Area under the plasma concentration versus time curve from time zero extrapolated to infinite time
aPPT	activated Partial Thromboplastin Time
AST	Aspartate Aminotransferases
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
C1D1	Cycle 1 Day 1
CDK	Cyclin-Dependent Kinase
CL/F	Apparent Clearance
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
C_{last}	The last quantifiable concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CSA	Clinical Study Agreement
CSF	Colony-Stimulating Factors
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P-450
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
EIU	Exposure In Utero
ER	Estrogen Receptor
FDAAA	US Food and Drug Administration Amendments Act

GCP	Good Clinical Practice
H_2RA	H_2-Receptor Antagonist
Hb	Hemoglobin
HEK293	Human embryonic Kidney 293
HER	Human Epidermal Growth Factor Receptor
HR	Heart Rate
Ht	Hematocrit
IC_{50}	Concentration of 50% Inhibition
ICD	Informed Consent Document
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
K_{el}	Rate constant for terminal phase
Ki	Inhibition coefficient
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LIP	Lead-in Phase
LSLV	Last Subject Last Visit
MAD	Maximum Administered Dose
MCL	Mantle Cell Lymphoma
MDCK	Madin-Darby Canine Kidney
MDR	Multiple Drug Resistance
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NA	Not Applicable
NCI	National Cancer Institute
NOEL	No-Observed Effect Level
ORR	Overall Response Rate
PCD	Primary Outcome Completion Date
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetic
PPT	Partial Thromboplastin Time
PR	Partial Response or Progesterone Receptor (depending on context)
PR	The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex.
PS	Performance Status
PT	Prothrombin Time
QD	Quaque Die (once daily)

QRS	The QRS complex is a name for the combination of three of the graphical deflections seen on a typical electrocardiogram. The QRS complex reflects the rapid depolarization of the right and left ventricles.
QT	Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QT_c	QT Interval Corrected for Rate
QTcF	The QT interval corrected for heart rate using Fridericia's fomula
RB/Rb	Retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RR	The interval between an R wave and the next R wave
R_{ac}	Accumulation Ratio
R_{ss}	Steady-state accumulation ratio
SAE	Serious Adverse Event
SCID	Severe Combined Immunodeficiency
SCLC	Small Cell Lung Cancer
SD	Stable Disease or Standard Deviation (depending on context)
SNP	Single nucleotide polymorphism
$t_{½}$	Terminal Elimination Half-life
T_{max}	Time for C_{max}
ULN	Upper Limit of Normal
V_z/F	Apparent Volume of Distribution

Appendix 2. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

CATEGORIZING LESION AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion patiented to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific

definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION.

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate. Progression has not been documented, and

  - one or more target measurable lesions have not been assessed;

  - or assessment methods used were inconsistent with those used at baseline;

  - or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure);

  - or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 1. Objective Response Status at each Evaluation			
Target Lesions	**Non-target Disease**	**NewLesions**	**Objective status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 2. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only		
Non-target Disease	**New Lesions**	**Objective status**
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Appendix 3. National Cancer Institute (NCI) common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (Version 4.0 date May 29, 2009) has been placed in the Study Manual for this protocol. Alternatively, the NCI CTCAE may be reviewed on-line at the following NCI website: http://ctep.cancer.gov/reporting/ctc.html

Appendix 4. ECOG Performance Status*

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

*As published in Am J Clin Oncol 5:649-655, 1982.

Appendix 5. Bone Marrow Reserve in Adult

***Adapted from R.E. ELLIS**: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961*

MARROW DISTRIBUTION OF THE ADULT

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM AND MANDIBLE	Head:			136.6		
	Cranium	165.8	0.75	124.3	13.1	**13.1**
	Mandible	16.4	0.75	12.3		
HUMERI, SCAPULAE, **CLAVICLES**	Upper Limb Girdle :			86.7		
	2 Humerus, head & neck	26.5	0.75	20.0	8.3	8.3
	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
STERNUM AND RIBS	Sternum	39.0	0.6	23.4	2.3	
	Ribs:			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
	4	18.6		7.4		
	5	23.8		9.5	7.9	**10.2**
	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
	12	4.6		1.8		
PELVIC BONES	Sacrum	194.0	0.75	145.6	13.9	
	2 os coxae	310.6	0.75	233.0	22.3	**36.2**
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		**3.8**

MARROW DISTRIBUTION OF THE ADULT (CONT'D)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
	Vertebrae (Cervical):			35.8		
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1	3.4	
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9		
	1 pair	10.8	All 0.75	8.1		
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
VERTEBRAE	5	13.4		10.1	14.1	**28.4**
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		
	Vertebrae (Lumbar):			114.1		
	1 pair	27.8	All 0.75	20.8		
	2	29.1		21.8	10.9	
	3	31.8		23.8		
	4	32.1		24.1		
	5	31.4		23.6		
TOTAL		1497.7		1045.7	100.0	**100.0**

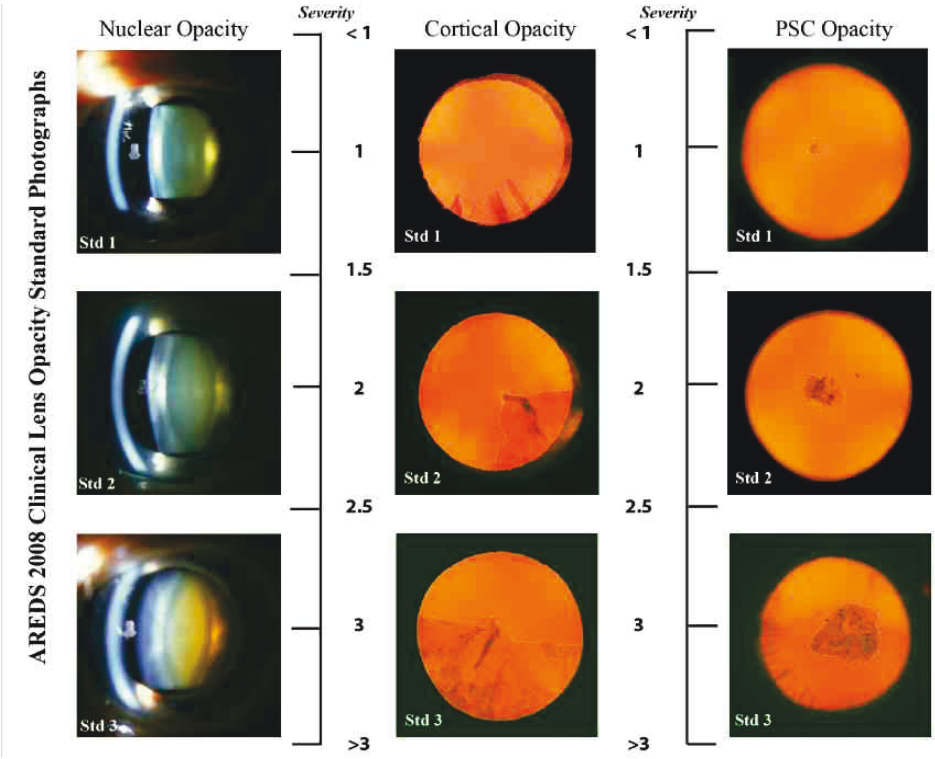
Appendix 6. List of Drugs Known to Predispose to Torsade de Pointes

Generic Name	Brand Name(s)
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®, E.E.S. ®
Flecainide	Tambocor®
Halofantrine	Halfan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Levomethadyl	Orlaam®
Mesoridazine	Serentil®
Methadone	Dolophine®, Methadose®
Moxifloxacin	Avelox®
Pentamidine	Pentam® NebuPent®
Pimozide	Orap®
Probucol	Lorelco®
Procainamide	Pronestyl®, Procan®
Quinidine	Cardioquin®, Quinaglute®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

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 7. Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading Procedure

- Dilate pupils to at least 5 mm diameter
- Use slit lamp with ~10X magnification
- Use brightest beam intensity
- Nuclear opacity
  - Orient beam at 45° to viewing axis
  - Adjust slit beam to standard parameters: 8 mm height and 0.3 mm width
  - Compare opalescence of nucleus with that in standard photos
- Cortical and PSC opacities
  - Select wide slit beam setting optimum for retro-illumination of lens
  - Visualize lens opacities against red fundus reflex background
  - Count only opacities definitely visible against red reflex
  - Mentally combine all cortical opacities into one contiguous area
  - Compare total opacity area with that in standard photos
- Classify each opacity with scale defined by 3 standard photos
- Select nearest half-step
  - Similar to standard or between two standards
  - Obviously less than mildest standard or greater than most severe


AREDS 2008 Clinical Lens Opacity Standard Photographs
Nuclear Opacity
Severity
< 1
1
1.5
2
2.5
3
>3
Std 1
Std 2
Std 3
Cortical Opacity
Severity
< 1
1
1.5
2
2.5
3
>3
Std 1
Std 2
Std 3
PSC Opacity
Std 1
Std 2
Std 3